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The Journal of Pediatrics

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THE RUBELLA PROBLEM

CLINICAL ASPECTS, RISK OF FETAL ABNORMALITY, AND METHODS OF PREVENTION

SAUL KRUGMAN, M.D., AND ROBERT WARD, M.D.
NEW YORK, N. Y.

PRIOR to 1941 rubella was considered to be a benign and unimportant disease of childhood. During the past thirteen years, however, it has been repeatedly indicted as a cause of congenital malformations in the newborn infant. The observations of Gregg[1] and Swan and associates,[2] of Australia, followed by reports from this country[3] and Great Britain,[4] have indicated that rubella in a pregnant woman may result in the so-called rubella syndrome in her newborn infant. This syndrome includes congenital cataracts, deafness, microcephaly, mental retardation, and congenital heart disease. Spontaneous abortions and stillbirths have also been attributed to maternal rubella infection.[5] Thus, this very mild disease of childhood may have serious consequences if contracted during the childbearing period.

During the past decade numerous newspaper and popular magazine articles have dramatized the potential crippling effects of rubella in the newborn infant. In the process of alerting the public to the hazards of this disease, these articles have tended to generate a great deal of anxiety.

Today, many physicians are concerned with the rubella problem. This problem has raised important questions about the management of the pregnant woman who either has been exposed to, or has developed, rubella. Should gamma globulin be given? How effective is it as a prophylactic agent? Is a therapeutic abortion indicated after the disease has been acquired? To answer these questions a physician should be armed with the following: (1) a knowledge of the clinical aspects of rubella; (2) a knowledge of the limitations of gamma globulin in prophylaxis; and (3) a knowledge of the risk of congenital malformations or stillbirth following maternal rubella infection. In this paper we shall discuss these three factors, and we shall attempt to answer some of the vital questions raised by the rubella problem.

CLINICAL ASPECTS OF RUBELLA

Rubella is frequently used as a "scrap-basket" diagnosis. Its iden-

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Presented before the Section on Pediatrics, The New York Academy of Medicine, April 8, 1954.

tification in the absence of an epidemic is difficult because of (1) the absence of a pathognomonic sign (like Koplik spots in measles), (2) the lack of a specific diagnostic test, and (3) the similarity to other diseases.

During one winter we had an opportunity to examine approximately thirty children who were reported as cases of rubella. We were unable to agree with the diagnosis in any of these patients. In our opinion some had measles with typical Koplik spots, others had mild scarlet fever, exanthem subitum, drug eruptions, papular urticaria, pityriasis rosea (one case), and bedbug bites (one case). In the following spring typical cases of rubella appeared. During the past six years we have been much impressed with the striking seasonal concentration of rubella in New York City during the spring months.

In our studies on rubella immunization[6] we have had an opportunity to observe the development and course of the experimental disease. It was produced by inoculating susceptible subjects with material containing active rubella virus. The incubation period was approximately twelve days (five days shorter than the naturally acquired disease). In all other respects the two were clinically identical.

A typical case of experimental rubella is illustrated in Fig. 1. Approximately seven days after exposure to the virus, a change in the size of the lymph nodes was noted. The nodes gradually enlarged and reached their maximum at the height of the rash. There was a slight elevation in temperature for approximately twenty-four hours; the rash disappeared in three to five days, and the lymph nodes gradually decreased in size over a period of two weeks or more.

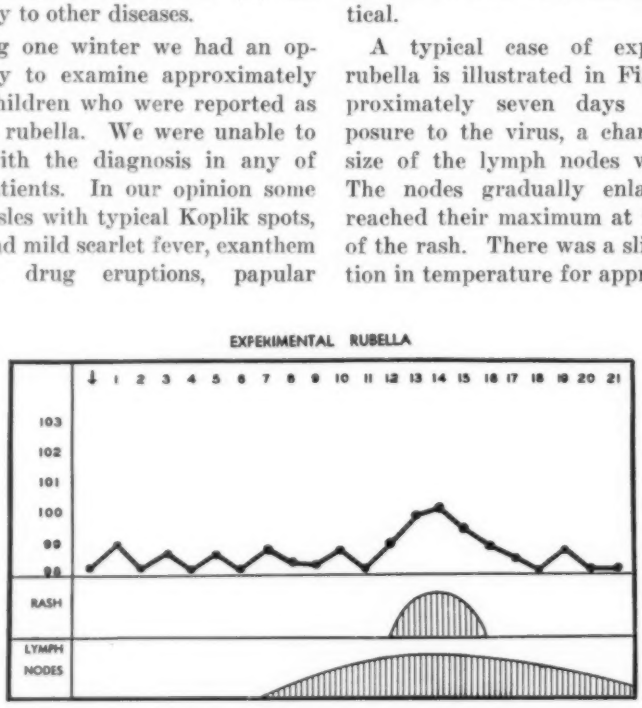

Fig. 1.—Diagram illustrating the clinical course of experimental rubella in man.

The variable clinical manifestations exhibited by thirteen patients with experimental rubella are listed in Table I. The maximum temperatures ranged between 99° and 101.6° F. There was no relation between the height of the temperature and the severity of the eruption. The rash, a generalized maculopapular eruption,

appeared on the face and neck first; then it spread to the trunk, and finally to the extremities. The more extensive eruptions subsided after three to five days; the milder ones cleared up in one to two days. Two of the patients (J. G. and P. K.) had no rash. Blood obtained from J. G. at the height of his fever was given intramuscularly to J. S. who developed typical rubella with rash thirteen days later. These findings proved that rubella can occur without a rash.

The most commonly involved lymph nodes were the posterior auricular, occipital, and cervical groups. Axillary, inguinal, and epitrochlear lymph nodes were also occasionally involved. As indicated in Table I the lymph nodes were markedly enlarged in three patients; in four they were moderately enlarged; in five they were minimally enlarged; and in one there was no enlargement.

The white blood count was not consistent. It varied between the normal range and a moderate leukopenia.

Our experience with naturally occurring rubella involving approximately 250 children and twenty adults confirmed the impressions gained from the cases of experimental rubella described above. The majority of the children (approximately 95 per cent) presented with the syndrome characterized by normal temperature or low-grade fever, three-day rash, and posterior auricular and occipital lymphadenopathy. A few patients had a temperature as high as 104° F. for twenty-four hours and an occasional one had no lymphadenopathy. In general the disease in adults was not as mild. Approximately two days before the onset of rash they developed malaise, anorexia, and were conscious of the enlarged and slightly tender lymph nodes. In contrast, the first obvious sign of the disease in children was the appearance of the rash. The lymphadenopathy preceding the rash in the children was apparently asymptomatic. Except for a transient polyarthritis in two adults, there were no complications in this group.

TABLE I. CLINICAL ASPECTS OF EXPERIMENTAL RUBELLA

SUBJECT	MAXIMUM TEMPERATURE, F.	RASH*	LYMPH NODE ENLARGEMENT*	LEUKOPENIA*
C. R.	100.4	+	++	0
J. G.	101.6	0	+	0
P. K.	100.8	0	++	++
N. K.	99.6	++	+	++
E. T.	101.6	+++	+++	0
K. L.	100.4	++	+	+
J. S.	99.0	++	+	0
S. E.	99.4	++	0	0
G. O.	99.8	++	++	0
C. N.	99.4	+++	+++	-
P. A.	99.6	+++	++	-
T. B.	99.2	+	+	-
M. I.	99.4	++	+++	-

*+++ = marked; ++ = moderate; + = minimal; 0 = none; - = not done.

The differential diagnosis of rubella includes a long list of infectious diseases and skin eruptions. Fig. 2 illustrates some of the differences between rubella, measles, exanthem subitum, and scarlet fever. The rash of measles is preceded by three to four

days of high fever, respiratory symptoms, and the development of the pathognomonic Koplik spots. Exanthem subitum, a disease of infancy, is characterized by three to four days of high fever followed by a rash which usually appears as the temperature falls to normal. In contrast, rubella characteristically has no prodromal period and the first obvious sign of illness is the appearance of the rash. Scarlet fever can be differentiated by the characteristic erythematous punctiform eruption associated with an acute exudative tonsillitis or pharyngitis from which group A hemolytic streptococci may be cultured. In separating rubella from the various skin diseases, the typical distribution and duration of the rash (three days), the low-grade fever, and the characteristic lymphadenopathy help to establish the diagnosis.

The enlarged lymph nodes are not specific for rubella. They may be associated with other infectious diseases and with acute or chronic infections of the scalp or upper respiratory tract. Routine examination of infants and children on our pediatric service reveals a sizeable number with palpable postauricular, occipital, and cervical lymph nodes. Thus, the development of a heat rash or other type of dermatitis may be mistaken for rubella in children who already have significant lymphadenopathy.

One attack of rubella probably confers a lifelong immunity. The majority of the so-called recurrent attacks of the disease reflect errors in diagnosis.

In reviewing the clinical aspects of rubella it becomes apparent that the diagnosis of this disease would present no difficulty in the face of an epidemic

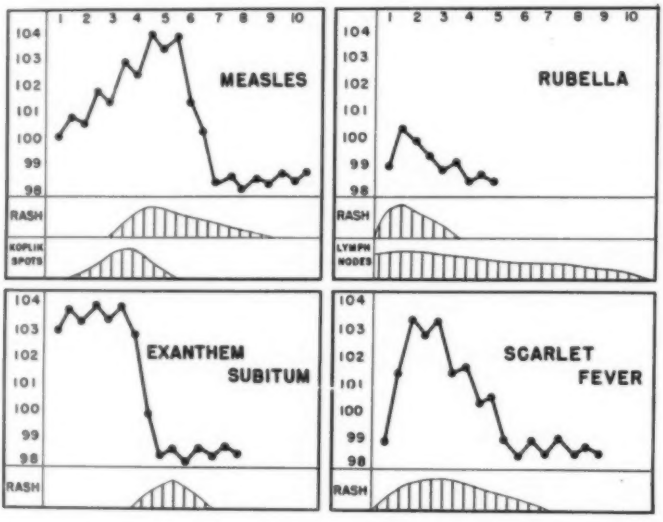

Fig. 2.—Diagram illustrating the clinical course of three infectious diseases which may be confused with rubella.

or known exposure. Under other circumstances, however, it may be necessary to observe the patient for two to three days before making a definite diagnosis.

EFFECT OF GAMMA GLOBULIN IN PREVENTION OF RUBELLA

In Table II we have tabulated the results of four studies on the prophylactic effect of gamma globulin on rubella. The Committee on Public Health of the New York County Medical Society reported a controlled study (No. 1) in an institutional outbreak.[7] Of 133 children who received approximately 0.1 c.c. of ordinary gamma globulin per pound of body weight, 8 (6 per cent) developed rubella. In contrast, 24 (18 per cent) of 129 controls came down with the disease. The committee summarized the findings as follows: "This committee believes that the evidence herein presented suggests that gamma globulin is of value in preventing German measles. However, some studies elsewhere are at variance with these results, so that further evidence must be collected before final conclusions are warranted."

Subsequently, Korns reported the results of his studies which were also conducted during an outbreak in an institution (No. 2). His findings indicated that there was an apparent variation in the efficacy of ordinary gamma globulin from lot to lot. In the first experiment (2a) 26 cases of rubella developed in both the control and treated groups with an identical incidence of 13 per cent. In the second experiment (2b), a different lot of gamma globulin was given. A clean-cut difference was observed; an incidence of 58 per cent in the controls as compared with 20 per cent in the immunized group. This could have occurred by chance alone only once in 10,000 times. In a third trial (2c) of a still different lot of ordinary gamma globulin, the incidence of rubella was

TABLE II. STUDIES ON PROPHYLACTIC EFFECT OF GAMMA GLOBULIN IN RUBELLA

SOURCE OF DATA	NO. OF INDIVIDUALS		MATERIAL INOCULATED		DEVELOPED RUBELLA	
	TEST	CONTROLS	GAMMA GLOBULIN	CONTROL	NO.	%
1. New York County Medical Society Committee on Public Health	133	129	0.1 c.c./lb.*	0	8 24	6 18
2. Korns						
a.	199	201	0.1 c.c./lb.*	0	26 26	13 13
b.	45	60	0.1 c.c./lb.*	0	9 35	20 58
c.	38	46	0.1 c.c./lb.*	0	11 18	29 39
d.	53	52	0.1 c.c./lb.*	0	0 0	0 0
3. Anderson and McLorinan						
a.	424 388	0	2 c.c.† 4 c.c.†	0	5 4 } 9	1
b.	15	9	4 c.c.†	0	8 3	52 33
c.	45	46	4 c.c.†	4 c.c. saline	3 7	7 15

*Ordinary gamma globulin.
†Convalescent gamma globulin.

39 per cent in the control group and 29 per cent in the immunized group. This difference was not statistically significant. The last experiment (2d) emphasized the vagaries of rubella and the vital necessity of controlled investigations. There were no cases of rubella in an exposed group of 36 adults and 17 children who had been immunized with gamma globulin. On the surface this seemed to be impressive. However, a comparable control group of 36 adults and 16 children also failed to produce a single case of rubella in spite of a similar exposure.

Anderson and McLorinan[9] of Australia conducted experiments (No. 3), utilizing gamma globulin prepared from convalescent rubella serum. In the first experiment (3a) 812 pregnant women were immunized with convalescent gamma globulin following reported exposure to rubella. Of these women 424 received 2 c.c. and 388 received 4 c.c. of the material. Although the low incidence of 1 per cent is suggestive of protection, the lack of controls renders the findings inconclusive. The authors themselves are the first to admit this. They say, "It is not known what proportion of women of childbearing age in Victoria was susceptible to rubella in the period of this survey." Korns' experience noted above has clearly demonstrated the potential hazards of evaluating an uncontrolled study of this type.

In the second experiment (3b) 24 volunteers were given 0.2 c.c. of garglings containing active rubella virus. Seventy hours later 15 of the volunteers were inoculated with 4 c.c. of convalescent gamma globulin. There was actually a higher incidence of German measles in the immunized group—8 cases (52 per cent) as compared with the 3 cases (33 per cent) in the control group.

The setting for the final experiment (3c) was a natural epidemic which occurred in a "group of adolescent males living together in a Melbourne suburb." A group of 45 boys who were given 4 c.c. of convalescent gamma globulin had an incidence of rubella of 7 per cent. In a control group of 46 boys who received 4 c.c. of saline, the incidence was 15 per cent. Although the result seemed suggestive, upon analysis it was shown to be not significant since it could have occurred by chance alone seventeen times in a hundred.

From the above studies, it is obvious that neither convalescent nor ordinary gamma globulin have proved to be consistently effective in the prevention of rubella.

THE RISK OF CONGENITAL MALFORMATIONS AND STILLBIRTHS

The risk of congenital malformations resulting from maternal rubella infection acquired during the first trimester of pregnancy has been variously estimated from 10 to 90 per cent. The large number of reports which have yielded this wide range in percentage have been of two types—retrospective and prospective. Much of the earlier data was accumulated by the retrospective method. In recent years, however, there have been several prospective surveys.

Retrospective Studies.—Wesselhoeft[3] in his review of rubella in 1947 summarized a large number of reports which included 521 congenitally deformed and 52 normal babies born of rubella pregnancies. This evidence has been interpreted by some as suggesting a 90 per cent risk. His re-

view of rubella in 1949[10] increased the number of congenital deformities to 656 and of normal babies to 124, thereby reducing the percentage to 80. The latter figures include many reports from Australia, England, and this country. The study by Miller and others[11] sponsored by the American Academy of Pediatrics was included in large part in the above review. Wesselhoeft wisely pointed out the inaccuracies of the retrospective type of investigation. His figures for the normal and congenitally malformed babies were accumulated from various unrelated studies. Consequently, it was impossible to calculate a specific risk. These retrospective studies were of value, however, because they indicated the potentially serious danger to the fetus following rubella infection in the first trimester of pregnancy.

Prospective Studies.—A few studies have been conducted by selecting the case before the child was born. Ingalls and Purshottam[12] summarized the results of their 19 cases which were pooled with 53 others. The total risk of stillbirth or deformity was about 17 per cent for infection in the first trimester. Tartakow[13] accumulated data on 20 pregnant women who developed rubella during an epidemic in Nassau County, New York, in the spring of 1949. Greenberg[14] collected 82 additional cases in a study conducted in New York City from 1949 to 1952. By pooling his data with that of other investigators, Greenberg was able to collect 83 cases complicated by rubella in the first trimester of pregnancy. Of these, 9 were stillbirths (10.8 per cent), and 5 were congenitally defective infants (6 per cent), yielding a total of 14 affected infants or approximately 17 per cent.

It is a remarkable coincidence that Lundström's[15] figure from the Swedish epidemic of 1951 was approximately 17 per cent also. This was a well-controlled prospective type of investigation. He compared the incidence of congenital malformations, stillbirths, and immaturity in a group of 1,067 women who had rubella in pregnancy with a group of 2,226 controls. The total incidence of 17 per cent following rubella acquired during the first four months of pregnancy was compared with an incidence of approximately 6 per cent in his control series. Lundström's figure of 17 per cent was not strictly comparable to Ingalls' and to Greenberg's because he included immature living infants (6 per cent). The omission of the immature infants from the data would change the incidence to 10.4 per cent in the rubella group as compared with 3.2 per cent in the controls. Thus the same 3 to 1 ratio would still be maintained.

Lundström makes the interesting statement that, in connection with the epidemic, 275 women underwent legal abortion after rubella during the first four months of pregnancy. Greenberg had a similar experience when he originally studied 34 cases of rubella acquired during the first trimester of pregnancy. Seventeen (50 per cent) of these cases had therapeutic abortions. We can only speculate on the possibility of an increased incidence of fetal abnormalities if these women had gone to term.

In analyzing the reported studies, it is important to consider the tendency to use rubella as a "scrap-basket" diagnosis. Consequently, some of the data of the prospective studies may have been obtained from "normal"

pregnancies. Under these circumstances, the task of making an accurate estimate of the risk is difficult and it must be deferred to the future when the results of well-controlled prospective studies may become available.

COMMENT

In the preceding discussion we have attempted (1) to clarify the clinical picture of rubella, (2) to evaluate the efficacy of gamma globulin in its prevention, and (3) to estimate the risk of congenital malformations in the newborn infant.

The rubella problem has highlighted the importance of making an accurate diagnosis of this disease. A child who has been labeled as having rubella may have exposed a household visitor or neighbor in the first trimester of pregnancy. The diagnosis made in a pregnant woman precipitates the fear of a possible stillbirth or deformed child. An erroneous diagnosis, therefore, may create unnecessary problems and complications for both the physician and patient.

How does one manage the susceptible pregnant woman who has either been exposed to or has developed rubella? Should gamma globulin be given routinely for prevention? Is therapeutic abortion indicated if the disease is acquired? In order to answer these crucial questions it is necessary to evaluate the importance of the following factors:

1. *Effect of Gamma Globulin:* The data presented above indicate that gamma globulin is not consistently effective as a prophylactic against rubella. Also there is some evidence that gamma globulin may modify the disease so that it may occur without rash. Warkany[16] told us of the case of a pregnant woman who was given gamma globulin following exposure to rubella. No apparent disease resulted but the baby was mentally retarded. It is conceivable that the mother had rubella without rash. Thus, the use of gamma globulin may give one a false sense of security.

2. *Risk of Congenital Malformations in the Newborn Infant:* As indicated above, the available information does not permit us to give a precise figure for the risk involved following rubella acquired during the first trimester of pregnancy. It would appear to lie somewhere between 10 and 90 per cent. The Swedish data derived from a controlled study would place the figure in the lower range. The extensive Australian experience[1, 2] points to a high percentage. In any event, we feel that there is ample evidence to indicate that the risk to the fetus is significant enough to warrant the recommendation of therapeutic abortion under *certain* circumstances. The risk following infection during the second and third trimesters of pregnancy does not appear to be significant.

3. *Personal and Family Considerations:* A variety of considerations may influence the management of the problem. For example, are there religious or other specific contraindications to abortion? Is this the first pregnancy of a healthy, young, recently married woman whose childbearing future appears bright? Or is the product of conception the result of fifteen years of effort by a childless couple in their forties?

Taking everything into consideration, it is obvious that the management of the rubella problem must be *individualized* in every case. There is

no simple formula for the solution. All of the factors listed above must be weighed very carefully by both the doctor and the patient. In the two hypothetical situations to follow, we shall describe our method of handling the problem.

A. In the case of the young, healthy, recently married couple, the decision to give gamma globulin would depend on whether or not they would consent to therapeutic abortion in the event rubella developed. If there were no contraindications to abortion, we would advise that gamma globulin be withheld in order not to mask the disease. If, on the other hand, the couple felt that they would not wish an abortion under any circumstances, then we would advise that gamma globulin be given.* In either situation, if rubella did *not* occur, then the pregnancy would be allowed to go to term. If the wife developed rubella, it would be the responsibility of the physician to inform the couple about the risk involved. The final decision should be made by the prospective parents.

B. The older couple, childless for fifteen years, in all probability would want to take the risk. Consequently, gamma globulin would be given and no abortion would be considered even if rubella developed.

In these two hypothetical situations, we have assumed intimate exposure to a definite case of rubella. On the other hand, if the contact had been casual, or the diagnosis questionable, then the management would have been modified accordingly.

The recommendations outlined above are based on our current evaluation of the available knowledge. At the present time, the most effective method of attacking the rubella problem is to encourage deliberate exposure to this disease before the childbearing period. This "active immunizing" procedure carries with it the danger of increasing the spread of German measles in the community. Consequently, it must be rigidly controlled in an effort to eliminate this hazard to the pregnant woman.

*In New York City "gamma globulin is distributed by the Health Department for use by physicians in pregnant women exposed to a case of German measles in their household. The dose is 0.1 ml. per pound of body weight, the maximum dose is 12 ml."

SUMMARY

1. During the past thirteen years rubella has been repeatedly indicted as a cause of congenital malformations in the newborn infant. Spontaneous abortions and stillbirths have also been attributed to this disease. This situation has created a "rubella problem" which has raised many important questions about the management of the pregnant woman who either has been exposed to or has developed rubella.

2. In an attempt to deal with this situation we have reviewed (a) the clinical aspects of rubella, (b) several studies concerning the effect of gamma globulin in the prevention of rubella, and (c) some of the data concerning the risk of congenital malformations or stillbirth following maternal rubella infection.

3. The clinical features of the experimental and natural disease have been described in detail. The importance of making an accurate diagnosis has been stressed.

4. Neither ordinary nor convalescent gamma globulin has proved to be consistently effective in the prevention of rubella.

5. An attempt has been made to assess the risk of fetal abnormality following maternal rubella infection.

6. The factors affecting the decision to recommend gamma globulin and

therapeutic (or prophylactic) abortion have been discussed with emphasis on the necessity to *individualize* each case.

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FURTHER OBSERVATIONS ON THE METABOLISM OF GALACTOSE IN INFANTS AND CHILDREN

ALEXIS F. HARTMANN, M.D., ERNEST E. McCOY, M.D., PAULINE A. SWARM, M.D., AND DORIS I. NAKASATO, B.S.
ST. LOUIS, MO.

THE observation[1] that evaluation of blood sugar, particularly with reference to the hypoglucemic state, frequently necessitated determination of galactose as well as glucose, raised a number of questions and prompted further study. Since transient partial "galactosemia" was found particularly in young infants with diarrhea from whose diets milk had been temporarily removed, the question arose—was the cause prolonged withdrawal of lactose from the diet, or was it the illness and attendant malnutrition?

To answer this question, we investigated, first, the metabolism of galactose in normal *newborn infants,* with the following results:

At birth and subsequently until appreciable amounts of milk were ingested, no galactose could be detected in the blood of normal full-term infants and then only very small amounts. Oral and intravenous galactose tolerance tests (Table I, Fig. 1) made during the first few weeks of life in such normal infants demonstrated excellent ability to metabolize galactose. After oral administration of the standard test dose of 1.75 Gm. per kilogram of body weight, the blood galactose rose from zero to a peak of 8 to 28 in from one-half to one hour, and then fell to a low level, sometimes again to zero, by the end of three hours. With a similar dose given intravenously as a 10 per cent solution, in five to ten minutes peaks of 79 and 90 were noted in two infants at one-half hour, with rapid falls to zero in three hours.

The simultaneous behavior of blood glucose proved especially interesting. Initial values, obtained always three to four hours after a feeding, again demonstrated the well-known lack of stability of blood sugar levels in newborn infants, ranging from a low of 25 to a high of 89 mg. per 100 ml. As orally ingested galactose entered the metabolism, it had a most striking effect on the levels of blood glucose. The lower values all rose sharply, then fell somewhat, then rose again, and finally stabilized. The intermediate values behaved similarly but with smaller swings; the highest values showed no initial rises, but instead declined to usual levels. At the end of three hours, all but one of the widely scattered initial values was to be found in the relatively narrow zone 49 to 66. The exception was the 3-day-old infant who was definitely hypoglucemic at the start. After a sharp rise in one-half hour from 25 to 73, the subsequent fall was not broken at the end of an hour, but continued to the very low level of 3 at two hours and was still only 5 at three hours. No definite clinical signs of hypoglycemia were noted at this time in this infant. From pre-

From the Department of Pediatrics, Washington University School of Medicine, the St. Louis Children's Hospital, and the St. Louis Maternity Hospital.

TABLE I. ORAL GALACTOSE (1.75 GM./KG.) TOLERANCE TESTS IN NORMAL INFANTS UNDER ONE MONTH OF AGE

NO.	NAME	SEX	WT. (KG.)	AGE (DAYS)	WHOLE BLOOD—MG./100 ML. BEFORE GALACTOSE		½ HOUR LATER		1 HOUR LATER		2 HOURS LATER		3 HOURS LATER	
					GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE
1	R.	F	3.7	2	0	52	15	74	8	47	8	49	8	49
2	M.	M	3.3	3	0	41	8	52	12	62	12	62	12	62
3	A.	F	4.0	3	0	48	16	68	16	34	15	58	0	54
			4.0	5	0	66	28	65	28	38	23	48	0	57
4	S.	F	3.4	15	0	57	15	68	7	62	7	53	7	53
5	V.	M	3.2	10	0	89	14	81	14	75	7	66	7	66
				21	0	68	12	41	13	61	13	51	7	—
6	P.	F	3.4	3	0	25	17	73	27	57	20	3	9	5
Intravenous Galactose (1.75 Gm./Kg.) Tolerance Test in Normal Infants														
7	G.	F	2.8	2	0	32	79	79	22	89	10	44	0	30
8	H.	F	5.0	4 mo.	0	39	90	50	15	50	8	47	0	45

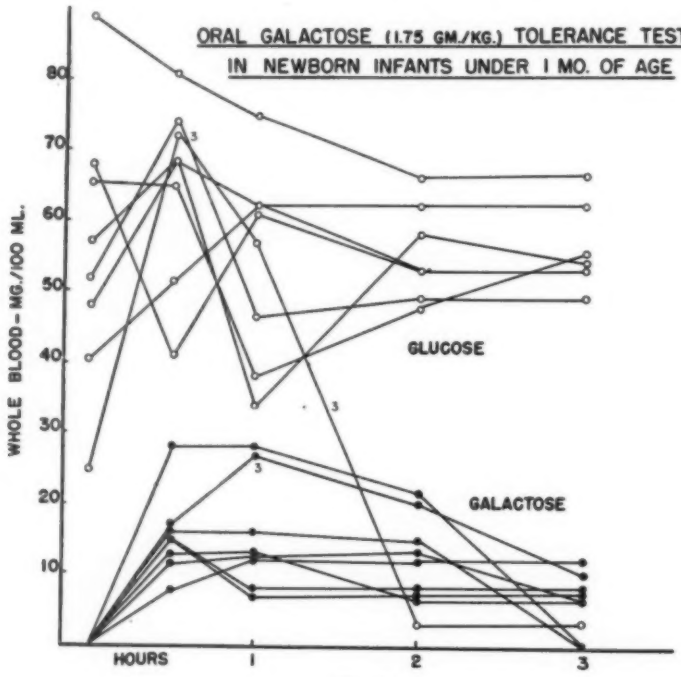

Fig. 1.

vious observations of insulin sensitivity of newborn infants, we would suspect that this infant was unusually sensitive and that the sharp initial rise of blood glucose stimulated insulin production.

It would seem, therefore, that the normal full-term infant possesses already at birth an excellent ability to metabolize galactose, despite the fact that in utero he had not been called upon to make use of it. It was, there-

TABLE II. ORAL GALACTOSE (1.75 GM./KG.) TOLERANCE TESTS IN NORMAL OLDER INFANTS

NO.	NAME	SEX	WT. (KG.)	AGE	WHOLE BLOOD—MG./100 ML.									
					BEFORE		½ HOUR LATER		1 HOUR LATER		2 HOURS LATER		3 HOURS LATER	
					GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE
1	Y.	M	5.4	10 wk.	12	62	32	61	41	61	3	61	3	64
2	M.	M	5.4	10 wk.	0	46	23	52	23	55	8	46	0	53
3	B.	M	5.0	3 mo.	0	50	8	50	8	49	0	53	0	52
4	S.	F	8.0	6 mo.	0	62	5	59	8	64	8	64	8	52
5	A.*	M	9.0	19 mo.	0	74	9	73	7	91	9	94	0	69

*No milk in diet for previous 12 months.

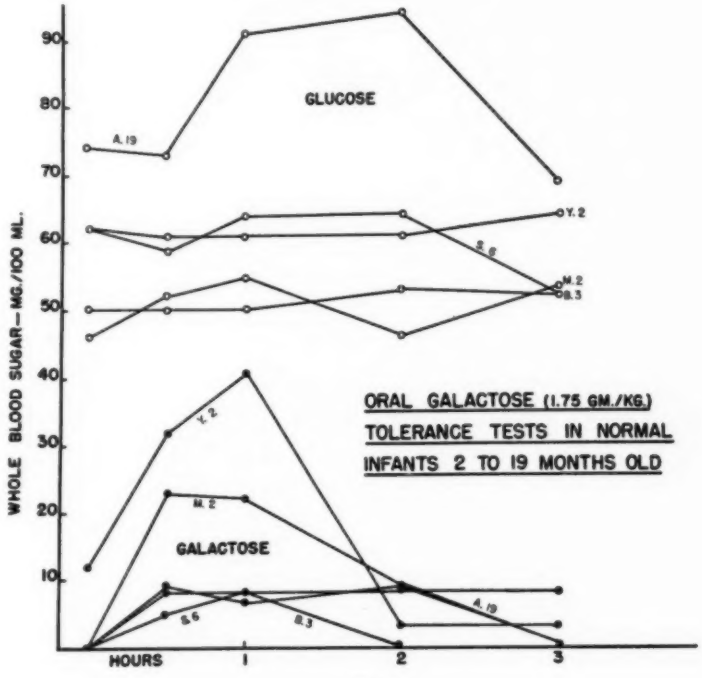

Fig. 2.

fore, not surprising to find that *normal older infants* also possessed excellent galactose tolerance (Table II, Fig. 2). In these older infants, stability of blood glucose had already been established, and metabolism of galactose had no appreciable effect on blood glucose levels.

Finally, it may be noted in Table II that the galactose tolerance test in 19-month-old Baby A. was quite normal despite the fact that the infant had received no milk in his diet for twelve months because of eczema thought to be due to milk sensitization.

It would also seem, therefore, that in the normal or near-normal infants, effective handling of galactose is not lost because of disuse, even over extended periods.

TABLE III. ORAL GALACTOSE (1.75 GM./KG.) TOLERANCE TESTS IN ABNORMAL INFANTS AND CHILDREN

NO.	NAME	SEX	WT. (KG.)	AGE	DIAGNOSIS	WHOLE BLOOD—MG./100 ML.									
						BEFORE		½ HR. LATER		1 HR. LATER		2 HR. LATER		3 HR. LATER	
						GALAC.	GLUC.	GALAC.	GLUC.	GALAC.	GLUC.	GALAC.	GLUC.	GALAC.	GLUC.
1	H.	M	2.1	4 da.	Prematurity	0	19	0	42	0	68	0	56	—	—
2	W.	M	1.5	26 da.	Prematurity	0	14	8	50	10	61	0	53	0	52
3	M.	M	2.0	5 da.	Prematurity	0	42	8	72	8	67	0	52	0	52
4	S.	F	1.9	40 da.	Prematurity	0	34	17	74	8	41	0	50	0	35
5	G.	M	3.8	22 da.	Erythroblastosis, mild; ACTH therapy	0	75	54	52	0	52	0	62	0	56
6	B.	M	11.6	20 mo.	Splenomegaly, cause undetermined	0	60	8	68	8	68	17	60	0	65
7	D.	M	3.4	5½ mo.	Malnutrition, poor diet	0	75	54	94	104	86	27	73	8	—
8	H.	M	6.0	5½ mo.	Postmeningitic hydrocephalus	0	69	14	60	22	77	17	74	10	53
9	S.	F	9.5	9 mo.	Chronic respiratory infection	0	36	10	60	29	71	31	70	0	60
10	H.	F	6.7	10 mo.	Otitis—mastoiditis	0	52	17	67	100	62	17	62	0	85
11	H.	M	8.3	11 mo.	Sickle-cell disease, bone lesions	10	60	2	62	5	66	10	61	7	67
12	A.	M	10.5	14 mo.	Bronchiolitis, convalescent	0	80	54	76	67	71	41	74	0	75
13	B.	M	13.2	22 mo.	Chronic respiratory infection	0	84	145	74	90	77	0	59	0	—
								(50 min.)		(80 min.)		(180 min.)		(300 min.)	
14	G.	F	61.9	12 yr.	Cirrhosis-jaundice, malnutrition	0	84	88	62	148	84	210	62	81	—

The question now raised is—what about *abnormal* young infants? Let us consider first the *premature* who has no obvious other abnormality. Oral galactose tolerance tests administered to four such infants from 4 to 40 days old and weighing from 1.5 to 2.1 kilograms (Table III) demonstrated excellent ability to metabolize galactose. Effect of stabilization of blood glucose was also seen in this group of infants, the two with fairly marked initial hypoglucemia showing rises of blood glucose to normal values.

Blood sugar findings, however, in a premature infant not doing quite well (Table IV) were extremely interesting and again pointed to the need for individual determination of glucose and galactose. This male infant, W. C., was born by cesarean section on Oct. 30, 1953, about eight weeks prematurely because of placenta previa and retroplacental abscess. The birth weight was 1,290 grams; no gross abnormalities were noted. After Coramine stimulation and a short period in the Air-lock resuscitator, respiration seemed normal, and color became good. Penicillin and streptomycin were administered prophylactically, and after administration of vitamins C and K, he was started on 5 per cent glucose by mouth. On the fourth day, Alacta feedings, without added sugar, were started. On the fifth day, because of slight dehydration and subnormal temperature, 20 c.c. of 5 per cent glucose was given intravenously. Subnormal temperature persisted. On November 7, the eighth day of life, the infant became deeply cyanotic for the first time, breathing ceased, and artificial respiration became necessary. After spontaneous respiration was again established, a blood for sugar was drawn. The total sugar was 34 mg. per 100 ml., expressed as glucose. Five hours later it was 0. Intravenous glucose was then given, and during the next two days subcutaneous glucose and fructose were administered and the Alacta formula fed by nasal tube. During this time the temperature continued subnormal. On November 10, Dextri-Maltose was added to the Alacta formula, and from then on there was general improvement—normal temperature, steady weight gain, and rise in blood sugar (Table IV).

TABLE IV. PREMATURE INFANT W. C.—WEIGHT 1.29 KILOGRAMS, BORN OCT. 30, 1953

DATE	TIME	WHOLE BLOOD—MG./100 ML.			REMARKS
		GALACTOSE	GLUCOSE	"TOTAL"	
11- 7-53	3:00 P.M.	—	—	34	**Clinical picture: On 11-7-53 a sudden attack of cyanosis and cessation of respiration, requiring resuscitation measures. Subnormal temperature from 10-31-53 to 11-10-53. Gastric tube and subcutaneous feedings required.**
	8:00 P.M.	0	0	0	
11- 9-53	10:00 A.M.	13	8	18	
	6:00 P.M. (before feeding)	8	0	6	
	45 min. after feeding	29	8	23	
11-10-53	10:30 P.M.	41	22	54	General improvement. Steady gain in weight. No untoward symptoms, but feeding still by tube.
11-20-53	Before feeding	22	46	64	
	1 hr. after feeding	20	81	97	

Inspection of the data reveals that this infant for a while had first, actual hypoglucemia of very great severity without hypergalactosemia and then, when tube-fed the milk formula, both relative and some actual hypergalac-

tosemia, masking the continued but milder hypoglucemia. Improvement, clinical and chemical, followed addition of the nonlactose-containing Dextri-Maltose to the milk formula. This infant behaved in a fashion very similar to the infants with diarrhea previously reported, the like of which we have continued to see.

In other infants of varying ages (Table III) with various degrees and types of abnormalities, oral galactose tolerance tests frequently indicated some impairment of galactose metabolism, higher than normal peaks being noted, with also longer periods of galactosemia. The 12-year-old girl (No. 14), with jaundice and malnutrition on the basis of cirrhosis of the liver had a very diminished tolerance.

While the normal and abnormal children were being studied, another example of apparently true, idiopathic, persistent galactosemia was encountered at a very early age, and study of this patient revealed more concerning the presence of galactose in the spinal fluid and in the urine. This boy, R. N., was born spontaneously on Sept. 13, 1953, after a full-term uneventful pregnancy. No vitamin K was administered to the mother before delivery or to the infant afterward. The baby seemed quite normal at birth and nursed the breast in a normal fashion. Jaundice was noted on the second or third day. Stools were of a normal yellow color. On the seventh day he vomited a considerable amount of blood and then continued to vomit smaller amounts, because of which he was admitted to the hospital on September 22, the tenth day of life.

The initial examination revealed an intensely jaundiced infant with dried blood in the nares and throat. The blood picture was abnormal only in a slightly prolonged bleeding time and leukocytosis of 28,450 with left shift. Ecchymoses developed at the sites of venipuncture. The Coombs test was negative, and blood typing of patient, father, and mother excluded Rh incompatibility. No findings of infection were noted, although the umbilicus grew *Esch. coli* on culture. The blood culture proved sterile. The liver extended three fingerbreadths below the costal margin, and the tip of the spleen could be palpated. The original impression was hemorrhagic disease of the newborn and unusually severe physiological icterus. With vitamin K administration, fresh blood transfusion, and antibiotics, the bleeding was promptly controlled, and the jaundice soon subsided and had disappeared completely by the time of discharge on Oct. 2, 1953.

The initial urine, however, revealed a 3 plus sugar reaction, which persisted during the first week of hospital stay and while the infant continued to receive milk, disappearing upon withdrawal of milk from the diet. Investigation of galactose metabolism was begun on the third hospital day with findings as noted in Table V and Fig. 3. The first blood sugar determination on Sept. 24, 1953, revealed 46 mg. glucose and 42 mg. galactose. Two days later the galactose was 127 and the glucose 31. On September 28 a standard oral galactose tolerance test revealed a very diminished tolerance. With substitution of Mull-Soy for cow's milk on September 29, the galactose diminished rapidly in the blood and spinal fluid, and the infant was discharged as well on October 2. When seen a week later because of diarrhea, both urine and blood were completely

TABLE V. R. N., BORN SEPT. 22, 1953

DATE	TIME	WHOLE BLOOD MG./100 ML.		SPINAL FLUID MG./100 ML.		URINE MG./100 ML.
		GALACTOSE	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE
9-24-53		42	46			
9-26-53		127	31			
9-28-53	Before galactose	163	46			
	45 min. after	272	67			
	60 min. after	325	25			
	120 min. after	320	46			
	180 min. after	298	88			6780
9-29-53		115	68	114	21	
9-30-53	8 A.M.	20		17		136
	2:30 P.M.					118
10- 2-53		12	67	10		
10-14-53		0	57			

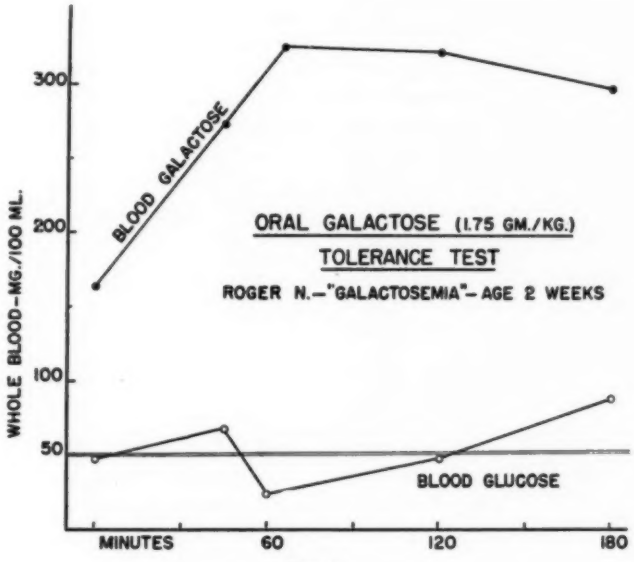

Fig. 3.

free of galactose. There was no jaundice or cataract formation; the liver edge was two fingerbreadths below the costal margin, and the cephalin cholesterol flocculation test was only 1 plus in forty-eight hours. At the time of this writing (Dec. 18, 1953), the infant, off of milk, has continued to behave normally.

Of special interest is the finding (Table V) that blood and spinal fluid galactose values were practically identical on the three occasions when simultaneous determinations were made. This finding was anticipated from observations made on the infant with "galactosemia" mentioned in the previous paper.[1] When that infant, R. T., was admitted to the hospital at the age of 2 weeks, a purulent meningitis, usually sterile on culture but twice growing *Pseudomonas aeruginosa*, was present, despite which the spinal fluid sugar was elevated and approximated

that of the blood which was approximately twice the usual value. The spinal fluid sugar then fell as the meningitis was being recovered from, certainly a paradoxical situation, but explained by the assumption that the early high values were due to galactose and the later low values to the disappearance of galactose from the blood and reappearance of glucose with subsidence of infection.* These observations indicate that evaluation of spinal fluid sugar may also require independent determination of glucose and galactose.

less. To study further the handling of galactose by the kidneys, it was decided to apply the whole blood method of determination of total and yeast-fermentable sugar* to urine diluted as much as possible to avoid interfering substances, and to demonstrate simultaneously the presence of such sugars by paper chromatography.†

These studies, quantitative titrimetric determinations and qualitative demonstrations by paper chromatography (Table VI), suggest that no renal threshold exists for excretion of galactose, which can be detected in the urine

TABLE VI. URINE SUGAR DURING GALACTOSEMIA

SUBJECT	WHOLE BLOOD—MG./100 ML.		URINE—MG./100 ML.	
	GLUCOSE	GALACTOSE	GLUCOSE	GALACTOSE
A. No. 3 (Table I)	65-38	28-28	–	++
	38-48	28-23	–	++
	48-57	23-0	–	+++
G. No. 7 (Table I)	89	22	–	1480
	44	10	–	705
H. No. 8 (Table I)	50-50	90-15	–	1700
	47-45	8-0	–	430
G. No. 14 (Table III)	84	142	423	3290
	60	210	+	++++
R. N. (Table V)	88	298	–	6790
	–	20	–	136
	31	126	–	++++

In Table VI, it should also be noted that appreciable amounts of galactose are present in the urine when blood galactose is only 20 mg. per 100 ml. or at all blood levels. Heavy excretion of galactose in No. 14, the 12-year-old girl with cirrhosis, was accompanied by considerable loss of glucose, even

*During the past year, this infant has continued to have a diet without lactose (milk). Mull-Soy has been substituted with meats, fruits, vegetables, cereals, and vitamins. Approximately bimonthly check-up continued to reveal no galactosemia. On December 12, at the age of 13½ months, his weight was 22 pounds and height 28¼ inches. He could walk by holding onto things. The eyes seemed quite normal, with no evidence of cataract, and mental development seemed normal. The liver edge could still be palpated one to two finger-breadths below the costal margin. A fasting standard oral galactose (1.75 Gm. per kilogram) tolerance test revealed the following: Before galactose ingestion, whole blood glucose 56, galactose 0 mg. per 100 ml.; after one-half hour, glucose 63, galactose 73; after one hour, glucose 56, galactose 224; after two hours, glucose 55, galactose 144; after three hours, glucose 43, galactose 112. It is evident, therefore, that this child still is unable to metabolize galactose normally, although the curve is less high and prolonged than that of Feb. 10, 1953. Because an early diagnosis was made and lactose promptly removed from the diet, he seems to have escaped permanent injury and to be developing normally.

*A slight modification from our original procedure has become necessary. As the weather became warm, we noted that yeast washed with distilled water lost ability to ferment glucose satisfactorily, probably because of leaching out of mineral. Washing with Ringer's solution proved satisfactory. A final 20 per cent suspension of washed yeast in Ringer's solution was then substituted for the original 10 per cent suspension in distilled water. The method now is to lake the red cells of 0.2 ml. capillary whole blood with 2.8 ml. distilled water, add a 3 ml. quantity of the 20 per cent yeast suspension, and after five minutes the zinc sulfate and sodium hydroxide reagents to a final 1:40 dilution. As an additional safeguard, all runs are made with a known solution of glucose equivalent to blood containing 50 mg. per 100 ml. and a known solution of galactose equivalent to blood containing 25 mg. per 100 ml. Properly active yeast should give a zero value in the case of the glucose standard, and allow complete recovery in the case of the galactose standard.

†Butanol-pyridine-water was used as the solvent and aniline, ethanol, and oxalic acid as the spray.

though blood concentrations of the latter were well below the usual threshold.

SUMMARY AND CONCLUSIONS

Further studies have been made relative to the handling of galactose by normal and abnormal infants and children which permit the following conclusions:

1. Both full-term and premature infants, if otherwise normal, can metabolize galactose normally at birth.

2. Protracted withdrawal of lactose from the diet of a normal child does not lead even temporarily to deficiency in metabolizing galactose.

3. Many varieties of illness can lead to some deficiency in the utilization of galactose. Infections, malnutrition, and liver damage seem chiefly responsible.

4. Some premature infants, failing to do well, may be found to have severe hypoglucemia, masked by galactosemia, and resemble the young infants with diarrhea previously reported. The metabolic defect seems linked with malnutrition and, possibly, immaturity of development.

5. In normal newborn infants, galactose exerts a marked stabilizing effect on blood glucose.

6. Galactose diffuses readily into the spinal fluid, and its concentration there tends to equal that in the blood. Evaluation of spinal fluid sugar, therefore, may necessitate separate determination of glucose and galactose.

7. Galactosuria occurs regardless of blood concentration, but increases with rising blood values. When extreme, there may be associated glucosuria, despite normal or even low blood glucose concentrations.

REFERENCE

1. Hartmann, A. F., Grunwaldt, E., and James, D. H., Jr.: Blood Galactose in Infants and Children, J. PEDIAT. 43: 1, 1953.

ERYTHEMA MULTIFORME EXUDATIVUM TREATED WITH CORTISONE OR ADRENOCORTICOTROPIC HORMONE

Report of Four Cases

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FOUR cases of erythema multiforme exudativum (Stevens-Johnson syndrome) in children, treated with cortisone or adrenocorticotropic hormone, are presented, first, because of our dramatic results with hormone therapy, second, because of the young age group, and third, because of the sudden increase in incidence of this rare clinical entity, the four cases occurring within nine months.

This clinical entity, erythema multiforme exudativum (Stevens-Johnson syndrome) is characterized by any type of erythematous rash from the iris to the bullous type and may involve any of the mucous membranes of the body: severe stomatitis, conjunctivitis, bronchitis or bronchopneumonia, balanitis, urethritis, vulvovaginitis, and, rarely, acute gastroenteritis or endocarditis. It is accompanied usually by severe constitutional reactions, which include hyperpyrexia, marked toxicity and prostration, and often generalized edema.

A review of the literature has been made. Stevens and Johnson[1] in 1922 reported two cases, in a 6-year-old male and a 7-year-old male, of the "new eruptive fever associated with stomatitis and ophthalmia, a syndrome of dramatic onset with fever, conjunctivitis progressing to panophthalmitis, and cutaneous eruption, with prostration." One patient became totally blind, and the other had corneal scarring in one eye.

Von Hebra's[2] disease had been described in 1860 as erythema multiforme exudativum with stomatitis and purulent conjunctivitis, but with less severe constitutional reactions than those seen by Stevens and Johnson.

Ashby and Lazar[3] reviewed eighty-one cases of erythema multiforme major occurring from 1860 to 1951, reporting four new ones of their own and reviewing seventy-seven cases previously reported in the German, French, English, and American literature. Soll's[4] very detailed review of twenty-two cases and report of twenty cases in 1947 are included in Ashby's analysis.

In the eighty-one cases reported by Ashby and Lazar no specific etiology was found.

The majority of cases occurred in males. It was rare in children, two occurring under 3 years of age and twenty under 10 years. All of the cases had skin lesions; 100 per cent stomatitis; 91 per cent conjunctivitis; 100 per cent inflammatory lesions of the external genitals, balanitis, or vul-

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vovaginitis; rarely with gastrointestinal symptoms; rarely with electrocardiographic changes; 29 per cent with bronchitis or pneumonitis. The course was self-limited to an average of two to three weeks. The mortality was 10 per cent in his series. The prognosis is guarded in regard to severe eye complications. Sixty per cent were totally blind. No therapy was found to be specific. Twenty-three received sulfonamides, thirteen penicillin and sulfonamides therapy combined. The others were treated prior to the use of the sulfonamides.

Since then, Aureomycin, penicillin, and Chloromycetin have been used for therapy.

Since Ashby's and Lazar's report, Wright and Jenkins[5] reported two cases in Negro males, 3 and 5½ years old. Both were treated with Aureomycin.

One case in a 5-year-old male was reported by Romer,[14] in which there was marked involvement of all the nail beds and subsequent loss of all the nails. He was treated with penicillin. A severe case in a 10-year-old male reported by Davies[15] was treated with antibiotics without improvement of the conjunctivitis until local cortisone was used.

Only two cases in adolescence were treated with ACTH or cortisone. A 14-year-old Negro male, reported by Agostas and associates,[8] was treated successfully in his third attack of erythema multiforme bullosum with cortisone intramuscularly. After forty-eight hours of therapy the lesions were dry and almost healed. A 16-year-old male, critically ill with erythema multiforme exudativum, reported by Van der Meer and co-workers,[16] was treated with ACTH with a dramatic response. All lesions healed in four days.

Other cases reported since 1951 treated with ACTH or cortisone were in adults reported by Finn and MacGillivray,[6] Wammock and associates,[7] Falsone and collaborators,[9] and Caldwell.[17]

In the older literature the eye complications were more frequent and more severe. In 1935 Ginandes[11] reported a case in a 5½-year-old who required enucleation of one eye. Rutherford[10] in 1929 reported a case complicated with purulent endophthalmitis in a 27-month-old male, which also required enucleation of an eye.

CASE REPORTS

CASE 1.—S. R., a 6-year-old white male, was admitted to The Brooklyn Hospital on June 20, 1952, having been acutely ill at home for three days prior to admission, with high spiking fever, 101° to 105° F. At the onset of the illness he had generalized enlargement of the left posterior cervical chain of lymph nodes: they were hard, not red, not tender. The pharynx was moderately red, and increased in severity with increasing size of the left posterior cervical lymph nodes. He was given 450,000 units of penicillin daily for two days with 0.5 Gm. sulfadiazine every four hours. The night prior to admission, the patient vomited four times and complained of abdominal pain. The first hospital day he was continued on penicillin therapy. He was acutely ill, refusing fluids and complaining of abdominal pain. The second hospital day he still ran a spiking temperature to 104° F. A few small discrete, half-inch in diameter, pink nonelevated skin lesions were noticed on his palms, legs, and right axilla. His lips were dry. A mild conjunctivitis was noted. His only complaint was abdominal pain. He had vomited once during the night.

He was critically ill. An infusion was started to restore fluid balance. By the third hospital day a surgical consultation was necessary because of the persistence of abdominal pain and a generalized distended, tender abdomen. Conjunctivitis had increased. On the fourth day his eyes became puffy and face swollen, scrotum red and tender. The abdomen was still tense and distended but with no localized tenderness. The child showed increasing hyperirritability. A short systolic blowing murmur had developed at the fourth space at the left sternal border. The neck was moderately stiff. A lumbar puncture was done. The cerebral spinal fluid was normal. Posterior cervical glands were still enlarged and tender. Conjunctivitis and edema of eyelids persisted. There were several areas of erythema of the iris type. Four loose, watery, tarry stools developed in the late afternoon of the fourth day. The clinical impression was one of septicemia with ruptured appendix. Not until the next day, the fifth hospital day, was the diagnosis of erythema multiforme exudativum made. The increasing number of iris lesions, the increasing stupor and lethargy, the acute gastroenteritis, the edema, the acute conjunctivitis, the mild stomatitis, the heart murmur, a bullous lesion on the scrotum, supplied the diagnostic criteria. ACTH was started at once. He had been on intravenous Terramycin, oral Terramycin, penicillin, and streptomycin, none of these antibiotics changing the clinical course. He was given ACTH intramuscularly 25 mg. every six hours for four doses. Within twelve hours the temperature had dropped to normal and there was a dramatic clinical improvement. He became more alert; the edema and conjunctivitis began to subside. Because of the recurrence of tarry stools, ACTH was discontinued on the second day of therapy and on the sixth hospital day. There was one temperature rise the next day to 101.6° F. and after that he remained afebrile until his discharge on the twentieth hospital day.

The erythema and swelling and bullous lesion on the scrotum had cleared by the seventh hospital day and there was no conjunctivitis present. Hospitalization was continued because it was felt a toxic myocarditis existed: poor quality heart sounds; persistence of systolic murmur; elevation of the sedimentation rate and electrocardiographic changes; prolonged atrioventricular conduction time, 0.18 sec. on successive electrocardiographs; no changes on cardiac x-ray or fluoroscopy on the eleventh hospital day. By the eighteenth hospital day his electrocardiograph was normal, the P-R interval was 0.12 sec. On discharge his general condition was good. The soft systolic murmur was hardly audible.

Laboratory data: Stools showed 4 plus occult blood; blood culture was negative. Urinalyses were normal; prothrombin time was normal; mixed febrile antigens were negative.

Six days after discharge his heart murmur disappeared and his heart sounds were of good quality. His sedimentation rate did not become normal for two months. In November and December, 1952, he had two mild attacks of pharyngitis which responded to penicillin. He put on weight and remained well until an acute pharyngitis with a few ulcerative lesions on the faucial pillars, and low-grade temperature occurred in July, 1953. It was ten days before these lesions healed. In September, 1953, he had a sore throat, a temperature of 101° F., and again several aphthous spots on his faucial pillars. These cleared in three days of oral cortisone therapy at home. He has no heart murmur and clinically is a well child. He has had no recurrence of any type of erythema.

CASE 2.—J. S., a 6-year-old white male, became ill rather suddenly with high temperature (104° F.), sore throat, edema of face, lips, fingers, and toes, enlarged cervical lymph glands, conjunctivitis, edema of the testicles, and large bright red circinate lesions on his trunk and buttocks. He de-

veloped painful elbow and finger joints.

A diagnosis of Stevens-Johnson syndrome was made at home, and cortisone 25 mg. every four hours was begun. In twelve hours there was a drop in temperature from 104° to 100° F. and the conjunctivitis began to clear. By thirty-six hours the rash had markedly faded and the boy's general condition very much improved.

Then, due to a misunderstanding, cortisone was stopped, with a return of symptoms. The boy was admitted to the hospital on Dec. 29, 1952, with the symptoms as described above. However, the temperature was only 100.5° F. In the hospital, cortisone was begun again, 25 mg. every six hours and continued for five days with the same dramatic results as experienced at home. The dose was tapered off over the next four days. This time, however, after forty-eight hours all symptoms had disappeared without return.

He has remained well to date.

His past history is not remarkable.

The laboratory findings were essentially normal. Admission complete blood count was normal except for 12 per cent eosinophilia. Thorn test was 829 eosinophils per cubic centimeter on Dec. 29, 1952. Sedimentation rate on discharge was 2/6.

CASE 3.—J. E., a 14½-month-old Negro female, developed an upper respiratory infection with cough and high fever (104° F.). There was a running nose, also a sore throat. These symptoms persisted for three days during which time the child received intramuscular penicillin and oral sulfonamide therapy.

The night of the third day the mother said her baby was worse and had developed a rash, although she was coughing less.

The infant was admitted to the hospital that night, Jan. 22, 1953, and presented the following: rectal temperature of 105° F., fiery injected conjunctivae, edema of both eyelids, marked stomatitis, abdominal distention, and large red circinate raised lesions over the trunk, buttocks, and extremities. These were hot to the touch. There were enlarged axillary and cervical lymph nodes and tarry stools. Nose, throat, heart, lungs, neurological and funduscopic examinations were negative.

The diagnosis of Stevens-Johnson syndrome was made and 20 mg. of ACTH every six hours begun at once, following blood culture and eosinophile count. Twenty milligrams of ACTH every six hours was given for six days and then gradually reduced over the next six days.

Within twelve hours the temperature dropped, and by eighteen hours was 100° F. It remained under 100° F. except for one reading thereafter. In addition, the child was generally greatly improved. The rash was fading, the conjunctivae clearing.

Over the next three days improvement was maintained, and by the fifth day the rash was almost completely gone, conjunctivae were normal, and the lymphadenopathy was no longer present. The abdomen was flat and nontender, and stools were normal.

The stomatitis persisted and the white blood count rose to 32,000 with 89 per cent polymorphonuclear cells. Sternal marrow showed a general proliferation and this was felt to be due to ACTH. However, because of the stomatitis, ACTH was continued through the twelfth day of hospitalization. By the thirteenth day the mouth was almost normal.

Subsequently the child has been completely well to date. Follow-up blood counts and marrow smears showed normal findings.

The past history of this infant had been uneventful.

The laboratory findings were: Thorn test, 22 eosinophils per cubic centimeter; white blood count 12,400 with 87 per cent polymorphonuclear cells; elevated sedimentation rate, 22/10; sterile blood culture. Sedimentation rate on day of discharge was 4/12.

White blood count was still elevated, 26,000 with 79 per cent polymorphonuclear cells.

CASE 4.—W. R., a five-year-old white male, became acutely ill on Nov. 16, 1952, at home. He was first seen on Nov. 17, 1952. At that time he had a temperature of 102° F. and symptoms of an upper respiratory infection. He was given Aureomycin. Forty-eight hours later he developed marked conjunctivitis, stomatitis, edema of lips, polyarthritis and a peculiar, generalized rash, and mild bronchitis. The rash was circular with pale centers, of the iris type. At first appearance the child's face looked like a case of measles. However, the type of rash and joint pains ruled that possibility out. The child also had nausea and vomiting and a harsh cough. A tentative diagnosis of erythema multiforme exudativum was made. A member of the staff saw the child in consultation.

The patient was given cortisone 12.5 mg. every four hours. This dosage was gradually reduced over a period of two weeks. The response to cortisone was dramatic. In forty-eight hours the child was markedly improved and he was asymptomatic in one week. The cortisone was started on the sixth day of illness. He was also given salicylates to relieve the excruciating joint pains, especially the pains in the soles of his feet. The child had such severe pain that he screamed when touched or carried. Another interesting finding was marked desquamation and loss of fingernails during convalescence.

CASE 5 (Comparison Case).—R. B., an 11-year-old male, was admitted to The Brooklyn Hospital on Oct. 13, 1937. He had been ill for ten days at home with a mild upper respiratory infection, cough, and fever. Three days prior to admission, his mouth became very sore and he was unable to swallow. His temperature was elevated to 103° F. daily. He vomited and had generalized malaise. On admission his lips were swollen with hemorrhagic crusting. His gums were swollen and covered with a white exudate. He had a severe purulent conjunctivitis with swollen eyelids. He had fine moist râles at the right base. On the thirteenth day of his illness (third hospital day) he developed a typical rash of erythema multiforme exudativum and a severe urethritis. His course was stormy—a toxic, acutely ill boy with spiking temperature to 103° and 104° F. daily until the twenty-third day of his illness.

Treatment was symptomatic only, with a transfusion given on the sixth hospital day. The stomatitis cleared slowly, being still present on the eighteenth hospital day. The urethritis cleared by the seventeenth hospital day; the rash was clearing on the thirteenth hospital day. Slight conjunctivitis remained on the eighteenth hospital day. All signs of pneumonitis had not cleared until the twenty-fourth hospital day. Total length of illness was thirty-five days, of which he was hospitalized twenty-five days.

This case, reported by Rosenberg and Rosenberg,[12] has been added as a control because his stormy, severe, prolonged course, so clearly remembered by the staff, illustrates by comparison the dramatic response to ACTH or cortisone reported in the four previous cases.

DISCUSSION

In the review of the recent literature,* no cases in children have been reported since Wright and Jenkins' two cases in 1951 treated with Aureomycin. No cases of erythema multiforme exudativum in children who had been treated with ACTH or cortisone have been reported when these patients were treated.

In view of the dramatic results in adults with the use of ACTH by Wammock and associates and of cortisone

*Since April, 1953, when these cases were presented, two cases have been reported in children, as noted in the review of the literature.

TABLE I. SIGNS AND SYMPTOMS IN FOUR PATIENTS WITH ERYTHEMA MULTIFORME EXUDATIVUM TREATED WITH ACTH OR CORTISONE, AND A COMPARISON CASE

	CASE 1— S. R.	CASE 2— J. S.	CASE 3— J. E.	CASE 4— W. R.	COMPARISON CASE
Therapy	ACTH	Cortisone	ACTH	Cortisone	Transfusion
Age	6 yr.	6 yr.	14½ mo.	5 yr.	11 yr.
Stomatitis	*	0	****	****	****
Conjunctivitis	**	**	***	****	****
Rash, type:					
Iris	*	0	0	****	0
Maculopapular	0	0	0	0	0
Erythema multiforme gyratum	0	**	****	0	***
Bronchitis	0	0	**	*	0
Pneumonia	0	0	0		**
Angioneurotic edema	**	**	0	*	****
Melena	***	0	***	0	0
Gastroenteritis	****	0	*	0	0
Lymphadenitis	*	0	*	0	0
Polyarthritis	0	*	0	****	0
Myocarditis	**	0	0	0	0
Genitourinary signs:					
Pyuria		0	0	*	
Urethritis	0	0	0	0	***
Testicular swelling	**	**	0	0	0
Eosinophilia	0	**	0		0
Total leukocyte count elevated	**	*	****		***
Polymorphonuclear cells increased	***	0	***		**
Sedimentation rate elevated	***	0	**		

*Mild.
**Moderate.
***Marked.
****Severe.

TABLE II. RESPONSE TO ACTH AND CORTISONE THERAPY IN FOUR PATIENTS WITH ERYTHEMA MULTIFORME EXUDATIVUM

	CASE 1	CASE 2	CASE 3	CASE 4	COMPARISON CASE 1937
Therapy	ACTH	Cortisone	ACTH	Cortisone	Transfusion
Age	6 yr.	6 yr.	14½ mo.	5 yr.	11 yr.
Dosage Daily	25 mg. q. 6 h. I.M.	25 mg. q. 6 h. Oral	20 mg. q. 6 h. I.M.	12.5 mg. q. 4 h. Oral	
Total	100 mg.	750 mg.	700 mg.	400 mg.	
Day of illness therapy commenced	8	4	3	6	16
Number of days given	1	9	12	14	
Temperature dropped to normal in	12 hr.	12 hr.	18 hr.	24 hr.	29 da.
Day temperature remained normal after start of therapy	2	3	3	1	17
Day child became asymptomatic after start of therapy	16	4	13	7	34
Number of hospital days	20	10	14	0	25
Total days of illness	23	16	17	15	35

and ACTH by Agostas and co-workers in 1952, we decided to use ACTH in Case 1, S. R. The results were so dramatic that ACTH or cortisone seemed the therapy of choice and the one that should be used at once as soon as the diagnosis was made, and was used immediately on the next three cases. The first patient clinically was well by the tenth hospital day. The myocarditis necessitated the twenty days of hospitalization. The second patient was clinically well the seventh hospital day but was hospitalized for ten days. The third patient was hospitalized fourteen days, but was afebrile from the third hospital day. The exceptionally severe stomatitis was slow in healing. The fourth patient was clinically much improved in forty-eight hours and asymptomatic in one week.

We feel that as soon as the diagnosis of erythema multiforme exudativum is made, ACTH or cortisone therapy should be started at once, to arrest or lessen the severe toxic systemic symptoms and signs, to shorten the course of the disease, and particularly to prevent ophthalmitis, retinitis, or blindness. The usual precautions taken with such therapy should be used; continuation of antibiotics, watching electrolyte and fluid balance.

There can be a great variation in the clinical picture. In the older literature, Stevens and Johnson[1] in 1922, Rutherford[10] in 1929, and Ginandes[11] in 1935, there were more eye complications. In our series there were two cases with severe melena, two with gastrointestinal symptoms, one with signs simulating an acute abdomen, one with marked leukocytosis, one with increased granulohematopoiesis due to ACTH, three with edema, two with polyarthritis, one with desquamation and loss of fingernails, and one with myocarditis (systolic murmur, poor quality heart sounds, and changes in the electrocardiograph), all unusual symptoms and signs. The loss of nails has been reported in only one other case in the literature.[14]

Until the appearance of the rash, stomatitis, and conjunctivitis, there is a problem in differential diagnosis. Case 1 was thought to be septicemia and a ruptured appendix. After the development of the heart murmur, rheumatic fever had to be considered. In Cases 2 and 4 swollen and painful joints were present, but no cardiac involvement. In Case 3 measles had to be differentiated. But with the presence of erythema, stomatitis, conjunctivitis, there is little difficulty in making the diagnosis of erythema multiforme exudativum when associated with severe constitutional reactions. Often agranulocytosis, leukemia, Vincent's angina,[4] and infectious mononucleosis must be ruled out. A brief summary of a fifth case,[12] treated in The Brooklyn Hospital in 1937 by supportive therapy and transfusion only, is included. He was ill thirty-five days, and hospitalized twenty-five days, as compared with an average length of illness of 18.5 days for the four treated patients and average hospital stay of 14.6 days for the three hospitalized patients.

Since erythema multiforme exudativum is a self-limited disease, ACTH or cortisone seems to us to be the therapy of choice, to decrease the severity of the symptoms, to lessen risk of complications, to decrease the toxicity, and to drop the temperature within a few hours to normal.

If the Thorn test shows less than a 50 per cent drop in the total eosinophil count, there is not a normal-functioning adrenal cortex, and cortisone should be used. We used ACTH in the children who were too ill to take cortisone easily by mouth.

What the mechanism is, of the action of ACTH or cortisone causing this dramatic response in erythema multiforme exudativum, we do not know. Maybe it is a defense or protective mechanism against the stress of severe illness or infection, as described by Selye.[13]

SUMMARY

1. Four cases of erythema multiforme exudativum in children 6 years old and under are presented, two treated with ACTH, and two with cortisone.

2. There was a drop in temperature to normal within twenty-four hours after ACTH or cortisone was given.

3. There was a striking clinical improvement with diminution of toxicity.

4. There was a rapid decline of all clinical signs: stomatitis, conjunctivitis, edema, melena and erythema, varying with each case.

5. Average total length of illness was 17.7 days.

6. Average hospital days of illness were 14.6 for the three patients hospitalized.

CONCLUSION

This study shows that ACTH or cortisone is the treatment of choice in erythema multiforme exudativum and should be used as soon as the diagnosis is made.

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MODIFICATION OF MATERNAL AND FETAL EFFECTS OF RADIOIODINE BY PRETREATMENT OF THE MOTHER

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SINCE the original use of radioactive iodine as an indicator in thyroid physiology in 1939,[27] this isotope has come to be used extensively both in *diagnosis*[15, 47] and in *therapy*.[70, 71] It was first used in studies of hypothyroidism in childhood by Hamilton and associates[26] and by Quimby and McCune.[47] Thus one can expect accelerated use of this isotope as experience with it continues to be favorable.

There are only rare occasions in which the clinical radiologist considers the use of this isotope with a woman who is pregnant. Nevertheless, the present study was motivated by the desire to determine whether prior treatment of the pregnant animal with one or another of the so-called thyroid or antithyroid substances might alter the avidity of either the maternal or the fetal thyroid for radioiodine. Specifically, the question could be stated, "Will thiouracil, methimazole, or thyrotrophic hormone treatment of a pregnant mouse protect the offspring against the expected radioiodine damage to their thyroid glands when it is injected into the mother?"

This type of study involves several interrelated analyses. It is first necessary to determine the histological effect of each of the various substances used, and of radioiodine alone, on both the mother and her fetuses. Second, an analysis must be made of the radioiodine effect when the isotope is administered after treatment with one or another of the experimental drugs. The analysis must be both physiological, by means of immediate Geiger-Müller counter readings of retained radioiodine, and histological. The latter analysis was delayed for two months until the maximum effect could be studied.

MATERIALS AND METHODS

Adult female mice from 3 to 6 months of age, and of albino stock, were used throughout this study. The females were time-mated with stock males of the same strain and of known fertility and on the thirteenth day thereafter the pregnant females were isolated from stock. Beginning on the fourteenth day the experimental animals were injected for three consecutive days with thiouracil, methimazole, or thyrotrophic hormone.* On the eighteenth gestation day (two days after the termination of the treatment with the thyroid-affecting drugs) radioiodine, in the form of carrier-free NaI^{131}, was injected subcutaneously into some of the pregnant mice. Radioactivity in each mouse was determined immediately by means of the Geiger-

From the Radiological Research Laboratory, Columbia University.

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*This hormone was generously supplied us by Parke, Davis & Company of Detroit.

Müller counter. The maximum (initial) radioactivity contained in each mouse was considered as 100 per cent. Readings on succeeding days at least through the twenty-first day were taken under identical conditions. In those few instances when the litter was delivered early, counts could be made of mother and litter separately for two days following birth. Radioactive decay and excretion generally reduced activity so that counts were not significantly above background after the twenty-third day.

The counter tube was set at a constant position so that each mouse, or its litter, had the same geometrical relationship for all readings. The distance from the face of the tube to the animals was 20.5 cm. Each animal or its litter was restrained in a round, covered plastic fly box with inside dimensions of 1½ cm. depth and 6½ cm. diameter. Background counts were taken before and after each set of readings of experimental animals, in order to detect any possible contamination. These counts, which were always very low, were included in the final calculations.

For the histological study, the mothers and their offspring were sacrificed two months after the injection of the radioiodine. The thyroids were fixed in Bouin's fluid, sectioned at 5 μ, and stained with Masson's trichrome stain which gives excellent differential pickup by the various thyroid constituents. Previous studies had indicated that by two months after injection with this isotope one would expect histological damage if it is to occur at all.

The radioiodine used was carrier-free sodium iodide (NaI^{131}) obtained from the Pile at Oak Ridge, Tenn. The activity of each sample of radioiodine received from Oak Ridge was calibrated for activity by the isotope staff of this laboratory, under the direction of Dr. Edith Quimby. It was diluted with distilled water to a concentration of 100 microcuries per cubic centimeter. A subcutaneous injection of 1 c.c., or 100 μc. I^{131}, was made into the dorsolumbar region of each of the experimental mice designated.

The thyroid substances used were:

Thiouracil: This substance was used as propylthiouracil which came in tablet form weighing 0.05 Gm. per tablet. Each tablet was dissolved in 5 c.c. of distilled water, and 2 c.c. were injected subcutaneously to give a dose of 20 mg. per day for three consecutive days, beginning on the fourteenth gestation day.

*Tapazole:** Each tablet of this substance contained 0.005 Gm. and was easily broken into two equal parts. One part (2.5 mg.) was dissolved in 1 c.c. of distilled water and was injected entirely. This meant that for each of the gestation days, fourteenth through sixteenth, each mouse received 2.5 mg. of methimazole.

Thyrotrophic hormone: This drug was supplied in powder form, each milligram containing the equivalent of 13 Junkman units. A solution in distilled water was made so that 1 c.c. contained 0.38 mg. or 5 Junkman units.

Each day for three days, fourteenth through sixteenth gestation days, 1 c.c. (5 Junkman units) was injected subcutaneously into designated mice. In the earlier experiments it was found that this high dose caused high fetal mortality so that it was finally reduced to 1 Junkman unit per day for an ac-

*Trade name for methimazole or methylmercaptoimidazole.

cumulated dose of 3 Junkman units. This latter dose was well tolerated.

OBSERVATION AND EXPERIMENTAL DATA

Controls for this study consisted of untreated pregnant females and pregnant females injected with radioiodine but not previously treated with any of the thyroid substances described above. The 100 μc. of radioiodine never interfered with the normal completion of gestation and delivery as did the higher level (5 Junkman units) of thyrotrophic hormone.

Two counter readings were taken of each mouse immediately after injection with radioiodine, and again at twenty-four-hour intervals thereafter through the twenty-first day. On a few occasions when the two counts showed considerable difference, a third count was taken and the average determined. The background and the decay were both taken into account in all calculations given in Table I. The data therefore represent the percentage of iodine retained in relation to the total injected. Since the precise amount of radioiodine injected varied by a few microcuries between the mice, the data are given in terms of percentage of the total initially injected. The figures therefore represent the percentage of radioiodine retained (not excreted) by the mice.

It is readily apparent from Table I that a large portion of the injected radioiodine is excreted within the first twenty-four hours, but that considerably less is excreted by the pregnant mice which had been previously treated with the higher dose (5 Junkman units per day) of the thyrotrophic hormone. The injection of the lower dose (1 Junkman unit per day) of this hormone had little effect on radioiodine retention. In contrast, pretreatment of the pregnant mice with either thiouracil or methimazole seemed to aid in the excretion or elimination of the radioiodine from the pregnant mouse. The thiouracil-pretreated pregnant mice retained about half of the radioactivity found in the nontreated but pregnant controls. Methimazole pretreatment also aided in the elimination of I^{131}.

TABLE I. I^{131} RETAINED BY THE ADULT FEMALE MOUSE, EXPRESSED IN PERCENTAGE OF TOTAL INJECTED
PREGNANT FEMALES

GESTATION DAY	THIOURACIL (5)	METHIMAZOLE (5)	THYROTROPHIC HORMONE		CONTROLS	NONPREGNANT CONTROLS
			5 UNITS (3)	1 UNIT (4)		
18*	100%	100%	100%	100%	100%	100%
19	20 (9-27)	22 (12-42)	50 (48-52)	32 (16-45)	39 (35-45)	29 (12-49)
20	17 (12-20)	20 (11-42)	37 (32-42)	28 (13-45)	32 (28-36)	25 (13-42)
21	14 (10-16)	16 (10-32)	35 (32-37)	22 (10-32)	28 (23-32)	19 (5-31)

*Day of injection of radioiodine. While the amount injected was 1 c.c. calculated to contain 100 μc., the value of 100 per cent was determined by means of the Geiger counter under the identical geometrical conditions as was used for succeeding readings. Thus any slight variation in injection was accounted for.

Note: The number following the designation of treatment signifies the number of pregnant mice used. In the table itself, the percentage values are averages of all animals similarly treated while the numbers in parentheses indicate only the percentage range. The daily percentage values can be challenged on a statistical basis, particularly with the thiouracil- and methimazole-treated mice, because of the range in data obtained from five mice. Nevertheless, there is a consistent downward trend on succeeding days, for all data, and the percentage retentions as of the nineteenth day do have significance when mice of different treatments are compared. Thus, while the data may not be statistically adequate, they do substantiate the histological data which is qualitative and which follows.

With regard to the effect of pregnancy itself, the amount of radioiodine retained by the pregnant mouse exceeded that held by the nonpregnant controls on any particular day. Twenty-four hours after injection the nonpregnant controls had excreted about 71 per cent, while the pregnant mice had excreted some 61 per cent of the injected radioiodine. Even after three days the nonpregnant controls continued to lose more than did the pregnant mice. Pregnancy therefore caused a greater retention of radioiodine.

In Table II are shown the data relating to the radioactivity of the mother, as compared with her newborn litter, of animals variously treated. It will be seen that the offspring of the pregnant controls retained a relatively larger amount of the available isotope, with the single exception of those whose mother had been treated with 1 Junkman unit of thyrotrophic hormone. This means that the prior treatment of the mother with thiouracil or methimazole altered the distribution of I^{131}, diverting it from the offspring. In the pregnant control the mother and her litter divided the available isotope almost equally.

Combining these observations with those of Table I, it seems apparent that pretreatment of the pregnant mouse with thiouracil or methimazole causes greater excretion of this radioisotope and also greater protection of the fetus and newborn against retention of radioiodine injected into the mother. In other words, both thiouracil and methimazole depress the avidity of both the maternal and the fetal tissues (thyroids).

The initial drop (excretion or elimination) of radioiodine during the first twenty-four hours following injection was greatest in the thiouracil-treated pregnant mice (to 20 per cent) and least (to 50 per cent) in those treated with the 5 units of thyrotrophic hormone. Following this initial drop the thiouracil-treated pregnant mice showed a decelerated rate of loss but even by the twenty-first day the percentage of iodine retained by these mice as compared with the nonpregnant controls was quite different (14 and 19 per cent). In contrast with this the thyrotrophic-treated pregnant mice still retained about twice as much radioiodine. Pregnancy and pretreatment by thyrotrophic hormone each favored retention of radioiodine.

TABLE II. DISTRIBUTION OF I^{131} BETWEEN MOTHER AND OFFSPRING FOLLOWING VARIOUS PRIOR TREATMENTS*

	THIOURACIL (5)		METHIMAZOLE (5)		THYROTROPHIC HORMONE (1) 5 UNITS		THYROTROPHIC HORMONE 1 UNIT		PREGNANT CONTROLS (5)	
DAY	M†	O	M	O	M	O	M	O	M	O
20	74	26	67	33	69	31	48	52 (1)	54	46
21	72	28	57	43	69	31	61	39 (4)	56	44

*Here again we admit that data from five mothers and litters may not be statistically the most satisfactory; nevertheless we are more concerned about the relative values and qualitative effects on the glands and these data support the histological data to follow.

†"M" designates "mother" and "O" the "offspring," or the entire litter regardless of size. Numbers in parentheses refer to number of litters involved.

Note: While on the twentieth and twenty-first days the proportions of activity retained by the mother and her litter were the same for the 5 units of thyrotrophic hormone and essentially the same for thiouracil and the pregnant control, nevertheless these values relate to different total amounts of activity due both to excretion and to decay (see Table I). It is therefore suggested that in these instances and, in fact, in most of the data, the retained iodine may be rather closely bound, probably within the thyroid glands.

Thiouracil and methimazole not only favored initial excretion, but the retention of radioiodine three days after injection was less than for any other condition.

HISTOLOGICAL CONSIDERATIONS

The thyroid glands of mice at 2 months of age are essentially like those of older adults except possibly in overall size. The follicular epithelium is fully developed and functional, and the colloid is abundant and relatively heavy. (See Plate I, Figs. 1 to 3.) The thyroids of 2-month-old mice which had been exposed to radioiodine by way of the mother on the eighteenth gestation day show the necrotic changes previously described.[21, 22, 53-56, 64] The follicles are small and almost totally devoid of colloid. Such colloid as can be found is highly vacuolated. The related epithelium contains enlarged nuclei, vacuolated and swollen cytoplasm, and many dead cells. The interfollicular connective tissue appears to be more prominent (Plate I, Figs. 4 to 6.) From data of Table II it seems evident that the litter as a whole obtains slightly less radioiodine than is retained by the mother, and when this is further divided between the litter members, the amount to each of the offspring must be very small. It has been estimated[53, 54] that no single mouse offspring contained more than a maximum of 5 per cent of the originally injected radioiodine twenty-four hours following the injection. Nevertheless, the radioiodine appears to pass to the fetuses readily, and the fact that they have very young and incompletely differentiated thyroids at the eighteenth gestation day explains why the glands are so severely damaged. It is assumed that the radioiodine which brings about the necrotic changes reaches the young through the placenta since, by the time of parturition, the retained iodine (by both mother and her litter) has been reduced by excretion and decay to about 28 per cent. It is possible, however, that some radioiodine might get to the young by way of the milk after birth, but the amount would be inconsiderable under these conditions.

The thyrotrophic hormone studies were not entirely satisfactory because the original dose used (5 Junkman units per day) caused either fetal death or abortion and the lower dose used (1 Junkman unit per day) appeared to have little effect at all. Table I has shown that the higher dose of thyrotrophic hormone caused a greater retention of the radioiodine (suggesting stimulated activity) while the lower dose had virtually no effect. The histological study (Plate I, Figs. 7 to 9) shows considerable radionecrosis in the thyroid of the young mice at 2 months of age whose mothers had had thyrotrophic hormone prior to radioiodine, quite similar to that of radioiodine alone. This analysis is qualitative so that attention must be directed to the actual size measurements given below. It is suggested that the lower dose of this hormone had no measurable effect on the thyroid necrosis in the offspring caused by radioiodine given to the mother during gestation.

The thiouracil pretreatment of the mother had not only caused the maximum excretion of radioiodine by the pregnant mouse but also caused the mother to retain the larger portion of all available isotope (74 per cent).

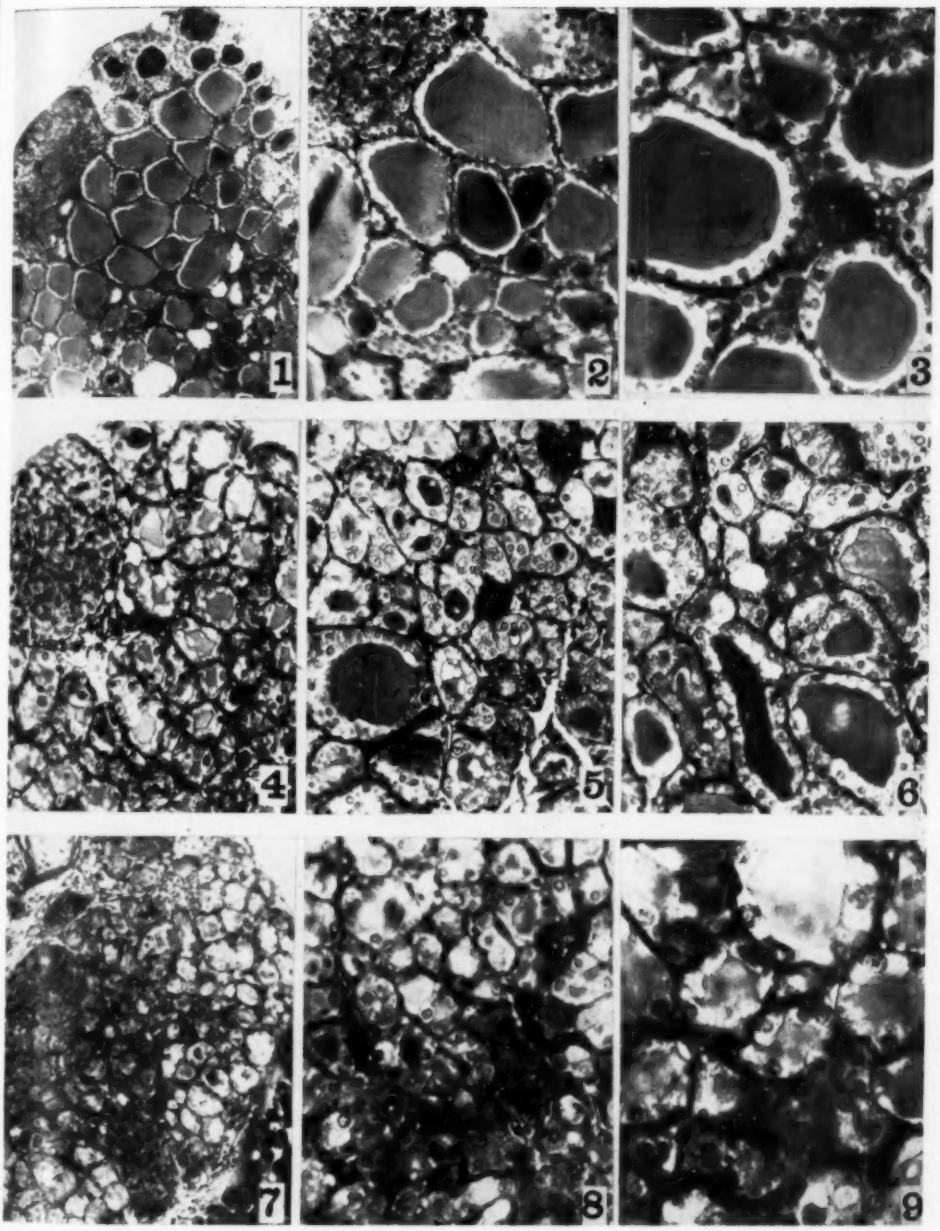


PLATE I.—MICE: OFFSPRING AT 2 MONTHS OF AGE.

Figs. 1, 2, 3.—Thyroids of controls, untreated.

Figs. 4, 5, 6.—Thyroids of mice whose mothers received 100 μc. I^{131} on the eighteenth gestation day. Note considerable destruction of follicular epithelium, sparse and vacuolated colloid.

Figs. 7, 8, 9.—Thyroids of mice whose mothers received three days of treatment of 1 Junkman unit of thyrotrophic hormone (fourteenth, fifteenth, sixteenth gestation days) followed by 100 μc. I^{131} on the eighteenth gestation day. Note destruction of epithelium, etc., quite comparable to Figs. 4, 5, 6. This low dose of hormone had effect of slight accentuation of radiation damage by I^{131}.

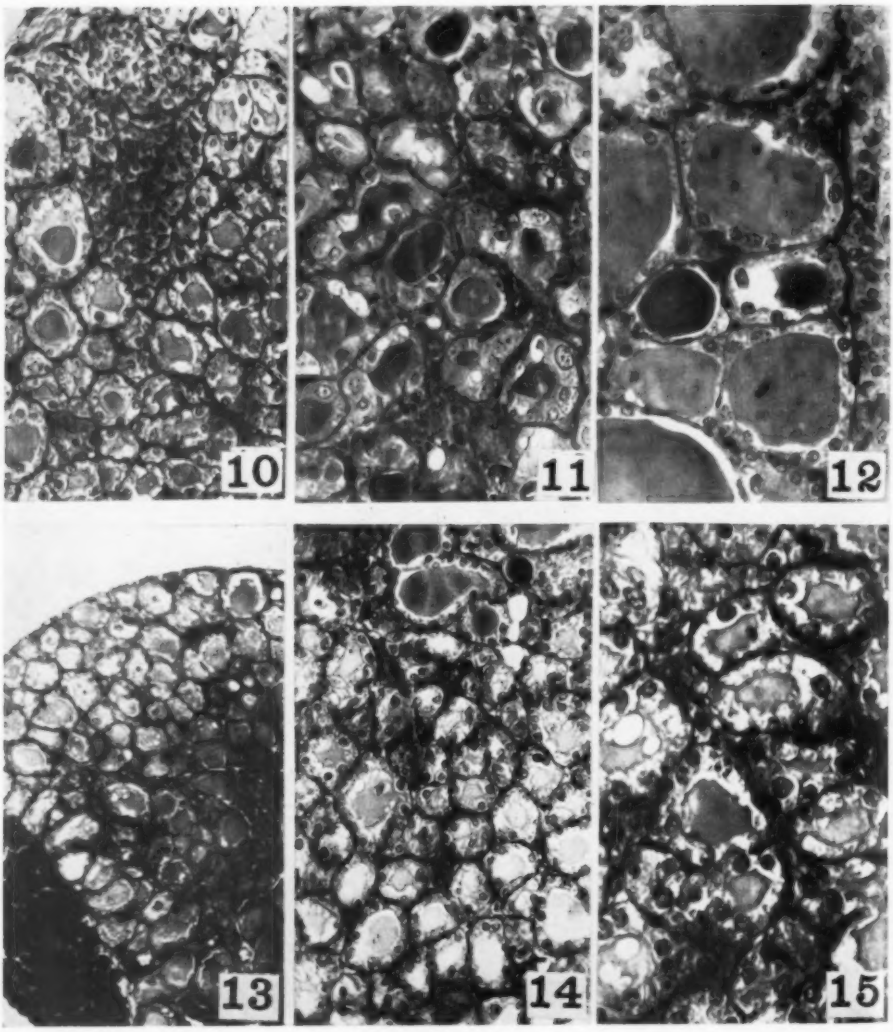


PLATE II.—MICE: OFFSPRING AT TWO MONTHS OF AGE

Figs. 10, 11, 12.—Thyroids of mice whose mothers were injected with thiouracil on the fourteenth, fifteenth, and sixteenth gestation days, and with 100 μc. I^{131} on the eighteenth gestation day. Note "protection" of thyroid against radioiodine damage by prior treatment with quite normal colloid and follicular epithelium (Fig. 12).

Figs. 13, 14, 15.—Thyroids of mice whose mothers were injected with methimazole on the fourteenth, fifteenth, and sixteenth gestation days, and with 100 μc. I^{131} on the eighteenth gestation day. Note "protection" of thyroid against radioiodine damage by prior treatment with methimazole during fetal stage, but not quite the degree of protection afforded by thiouracil.

These data are histologically verified by Plate II, Figs. 10 to 12, showing only slight radiation damage to the offspring thyroids at 2 months of age. The epithelium is desquamated in some of the follicles but is largely normal and there is abundant colloid. One should compare Figs. 1 and 10 or 3 and 12 to see how little damage has been incurred. This prior treatment of the mother with thiouracil definitely protects the fetal thyroid against radiation damage.

Methimazole, while causing the mother to excrete the isotope, and favoring her against her offspring in its retention, did not have quite the protective value that did thiouracil. This may have been due to the dosage, or to an actual difference in thyroid effect. Plate II, Figs. 13 to 15, shows thyroids considerably more "normal" than those treated with radioiodine alone (Plate I, Figs. 4 to 6) but not the healthy epithelium seen in Plate II, Figs. 10 to 12, of the thiouracil pretreated mice. Thus, methimazole protects the fetal thyroids but not as effectively as does thiouracil.

It should be stated here that while no illustrations are given of thyroids of offspring whose mothers were treated with the hormones alone, this is because there was no demonstrable effect as of 2 months of age. The treatment of pregnant mice with thiouracil, methimazole, or thyrotrophic hormone did have an immediate effect on injected radioiodine as shown in the excretion studies, but by two months after treatment there was no residual effect of the hormone treatment alone. However, those pregnant mice which had been given the combination treatment of thiouracil and then radioiodine had thyroids which showed considerable evidence of "protection" in that the necrosis was not as complete or extensive as in those treated with radioiodine alone. Many follicles were filled with normal-appearing colloid. It was pointed out (Table II) that in these mice the mothers kept most (74 per cent) of the iodine from their offspring. Nevertheless this still was less in absolute iodine than that retained by the untreated pregnant control mother, since she was not stimulated to excrete as much of the isotope. In absolute values the thiouracil-radioiodine mothers probably retained about 12 per cent (74 per cent of seventeen) of the injected iodine on the twentieth while those not receiving the prior treatment with thiouracil retained some 17 per cent (54 per cent of thirty-two). While this may not seem to be a large differential, it is a 35 per cent increment sufficient to bring the concentration of radioiodine to a level which results in almost complete ablation of the functional thyroid gland.

THYROID SIZE

Since all thyroid glands were sectioned serially at 5 μ, and every section was mounted and studied, it was possible to determine the exact dimensions of the glands under the various experimental treatments. For convenience in determining lobe length, one side was designated as the right as opposed to the other, or left side. There appeared to be some evidence that the left thyroid lobe was consistently a little larger than the right. However, these distinctions were simply used to avoid confusion. It can be stated that so far as total length of the two lobes of a single thyroid gland were concerned, there were instances

in which there was a difference of as much as 1,200 μ or 1.2 mm. This extreme case happened to be in a thiouracil-treated offspring where one lobe measured 1,435 μ while the other lobe measured 2,615 μ in length. In the majority of instances, however, the disparity in length between the two lobes was not more than 200 to 300 μ. The fact that there was any difference made it the more important that averages be taken, so that the table presents the extremes (indicating range) while the graph presents the composite averages.

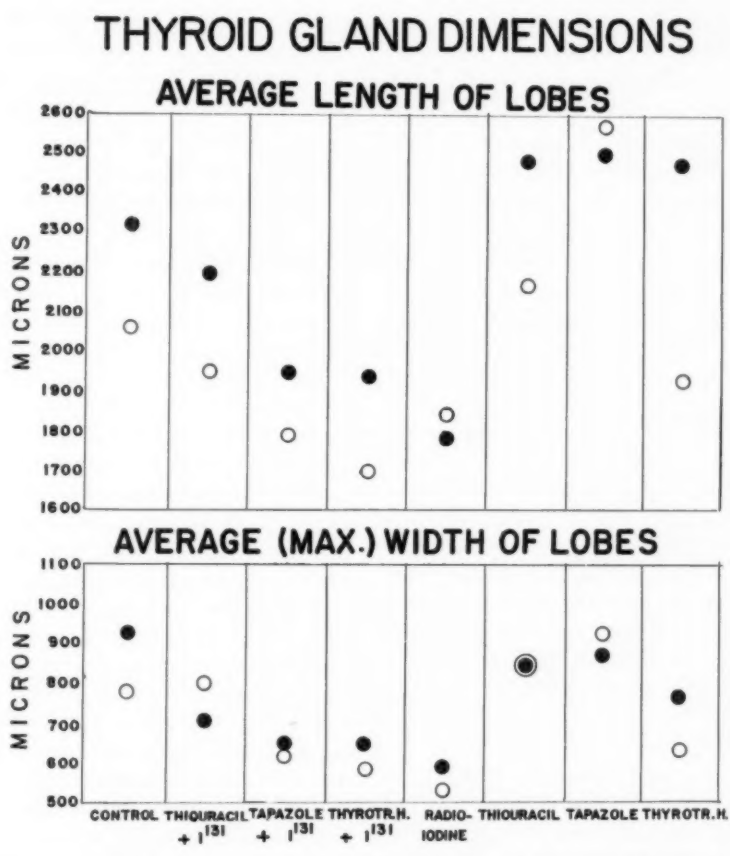
TABLE III. RECORD OF THYROID DIMENSIONS (IN MICRONS)

ANIMAL (TREATMENT)	LENGTH OF LOBES				WIDTH OF LOBES			
	MOTHERS		OFFSPRING		MOTHERS		OFFSPRING	
	LEFT LOBE	RIGHT LOBE	LEFT LOBE	RIGHT LOBE	LEFT LOBE	RIGHT LOBE	LEFT LOBE	RIGHT LOBE
Control	2,750	2,320	2,075	1,785	924	924	739	809
	2,420	2,100	2,285	2,095	878	970	832	739
	2,440	2,275			970	993		
	2,040	2,130			878	832		
	av. 2,309		av. 2,060		av. 921		av. 780	
Thiouracil + I^{131}	2,940	2,730	1,745	1,400	832	866	485	785
	2,715	2,260	2,480	2,515	785	809	878	809
	1,660	1,570	1,235	1,655	531	832	832	647
	1,690	2,015	2,605	1,925	578	416	855	1,109
	av. 2,198		av. 1,945		av. 706		av. 800	
Methimazole + I^{131}	2,795	2,360	2,145	1,970	809	832	693	693
	1,855	2,100	1,540	1,405	693	693	462	578
	2,160	1,660	1,940	1,715	554	554	739	601
	1,330	1,280	1,980	1,670	462	601	601	554
	av. 1,943		av. 1,796		av. 650		av. 615	
(1 unit) Thyrotrophic hormone + I^{131}	2,635	2,810	1,780	1,680	739	762	508	693
	1,375	1,310	1,820	1,635	531	739	485	705
	1,805	1,680	1,780	1,415	554	601	462	647
			1,770	1,720			601	554
	av. 1,935		av. 1,700		av. 654		av. 582	
I^{131}	1,670	1,895	1,735	1,535	554	508	462	462
	2,220	2,295	2,085	2,090	1,063	832	554	601
	1,535	1,225	1,910	1,535	300	439	554	554
	1,740	1,735	1,990	1,830	554	462	531	508
	av. 1,790		av. 1,839		av. 589		av. 528	
Thiouracil	2,120	2,085	2,615	1,435	785	832	878	1,109
	3,255	2,275	2,545	2,315	739	1,016	739	693
	2,870	2,215	2,130	1,995	739	855	832	785
	2,875	2,125			832	901		
	av. 2,478		av. 2,173		av. 837		av. 839	
Methimazole	2,630	2,315	2,630	2,225	693	785	970	1,016
	2,095	2,145	2,815	2,480	855	693	832	970
	2,630	2,205	2,415	2,840	832	924	924	832
	3,065	2,865			993	1,155		
	av. 2,494		av. 2,568		av. 866		av. 924	
(1 unit) Thyrotrophic hormone	2,450	2,380	2,115	1,785	832	809	647	554
	2,635	2,395	1,995	1,810	693	739	647	693
	av. 2,465		av. 1,926		av. 768		av. 635	

The data are presented in Table III and in Graph I for both the total length and for the maximum width of the lobes, following the various treatments. The measurements of the

maternal thyroids are shown in solid dots, and the offspring in open circles.

In analyzing the average data of Graph I it is readily apparent that the smallest thyroids of both the mother and her litter young are those that had received the radioiodine without any prior hormone treatment. These lobes measured about 1,800 μ in length and about 600 μ in maximum width, while the glands of the untreated controls were from about 2,050 to 2,300 μ in length or from about 780 to 970 μ in maximum width. This great reduction in size is related to the radiogenic necrosis previously described, but the



Graph I.—This graph is derived from histological material, serially sectioned and accurately measured. Each point represents the average of a minimum of at least four thyroid lobes, and some as many as eight. The solid dots represent the maternal and the open circles the offspring thyroids, each two months following the experimental treatment. This method of determining size changes is considered to be much more accurate than dissecting out and weighing the fresh glands, which are small and adherent to related organs.

size of the radioiodine-treated thyroids provided a base line for determining the effect of any prior treatment with a thyroid hormone.

The various treatments are arranged in such a sequence in Graph I that it shows the effect of treatment with the various thyroid compounds with and without subsequent treatment with radioiodine. It is obvious that thiouracil alone seems to afford protection in all cases against radioiodine reduction in size of the thyroid. Methimazole seemed to afford slight protection to the offspring, and thyrotrophic effect was so slight it is questionable. In the mice receiving hormone only, all the mothers showed longer thyroid lobes than even those found in the untreated controls. It is of interest that while these thyroids were consistently longer, even following thyrotrophic hormone, the increase in length was in the order of only 8 per cent two months after treatment. The same size relationships, with minor variations, are seen in the maximum widths of the lobes. Thus, in addition to the previously described histological changes in the various thyroids, actual measurements of the glands reflect modifying influences of the various experimental variables.

If one compares the sizes of the glands of the mothers after two months and offspring at 2 months of age, it appears that in the majority of instances the thyroids of the young mice are the smaller. However, there is one instance in which the glands of the offspring are longer and wider than those of the mothers, namely, two months after methimazole treatment of the pregnant mouse. This stimulation of the offspring thyroid to excess growth by methimazole was not reflected in an equivalent protection against radiogenic necrosis (methimazole plus radioiodine). This may mean simply that the growth-stimulating potency of methimazole is slower in manifesting itself and possibly more persistent in its effect. Certainly thiouracil pretreatment had demonstrably more protective value against radiogenic necrosis than did methimazole pretreatment.

Finally, reference must be made to Table IV which gives the detailed data from which the averages were determined to derive Graph I. It is obvious from an analysis of these data that in 50 per cent of the instances the size variable is not very much between different mice similarly treated. Largest size variations occurred in the animals treated with hormones alone. These which were subsequently treated with radioiodine did not show the same spread in size. This simply suggests that while hormone injection may be rigidly controlled, hormone absorption and utilization may vary from animal to animal. This is seen even in the thiouracil-treated offspring not treated with radioiodine. Such a situation is biologically significant and should be considered as individual cases, but the data here represent the average of the measurements of at least three mice for each category, and this means six lobe lengths. Thus, the average values fall into a very logical series as stated above.

DISCUSSION

Following the initial studies of Hertz and associates[27] radioiodine has been used extensively in clinical *diagnosis*[2, 9, 13, 16, 17, 20, 29, 33, 38, 39, 40, 45, 46, 48, 50, 57, 60-63] as well as in *therapy*.[4, 6, 8, 25,

[28, 31, 32, 41, 67] Some of the earlier uses of the antithyroid substances are referred to in papers by Astwood,[1] Williams and Bissell,[72] and Stanley and Astwood.[65, 66]

Recent experimental studies on lower vertebrates have indicated that thiouracil has an immediate and pronounced effect on the thyroid glands of the fish,[36] the frog,[7, 37] the salamander,[56] the chick,[3, 35, 44] and the guinea pig,[11] causing them to hypertrophy but to depress the uptake of radioiodine. In lower mammals Schulman[58] has described the metabolic fate of thiourea in the thyroid gland, and there have been related studies of these thyroid and antithyroid substances on liver phospholipid turnover,[14] adrenal weight and ascorbic acid,[18] the S^{35} deposition in articular cartilage,[12] and on the testes.[10] Nodular hyperplasia of the thyroid glands, following thiouracil treatment, was described by Laquer.[34] There appears to be some disagreement in regard to whether pretreatment of animals with thiouracil alters their metabolism to such an extent that they have a different sensitivity to x-irradiation. Blount and Smith[5] believe there is an increase in mortality due to metabolic stimulation. Haley and associates[23, 24] disagree and state that the potential sulfhydryl group in the thiouracil compounds' molecules is available for protecting the naturally occurring sulfhydryl groups in the animal organism and, as a consequence, there is an increase in survival time and a decrease in mortality of animals treated with thyroxin and thiouracil derivatives prior to x-irradiation. Thiouracil has been used in conjunction with radioiodine in the treatment of human hyperthyroidism,[38] of metastatic carcinoma,[49] and in the study of iodine uptake in experimentally induced thyroid tumors.[42] Montag[43] used the histological effect of thiouracil on the thyroid follicular epithelium to study the nuclear changes brought about by x-irradiation.

Rawson and co-workers[51] were among the first to study the uptake of I^{131} in animals made goiterous by thiouracil but this was followed by similar studies of Vanderlaan and Bissell,[68] by Stanley and Astwood,[65, 66] Reiss and associates,[52] Williams and collaborators,[73] Johnson and Albert,[30] D'Angelo and co-workers,[11] Schultz and Jacobson,[59] and Verzar and Vidovic.[69] Thus much information is available on the effect of thiouracil on the normal thyroid and in conjunction with ionizing radiations. None of these studies dealt with the effects on the fetus. No studies appear to be available on the effect of thyrotrophic hormone or of methimazole and radioiodine. Methimazole is a relatively new antithyroid compound which apparently has an effect on the rodent thyroid somewhat different in degree from its effect on the human thyroid, at least with respect to interpolated dosage.

This present study has revealed a rather high tolerance level of the pregnant mouse for thiouracil and methimazole but a different sensitivity for the thyrotrophic hormone. Initial estimates of 5 Junkman units per day were quite intolerable, the mice developing skin erosions at the site of injection and inevitable abortion or resorption of the fetuses. In one case only was there a normal delivery, but the litter was shortly eaten by the mother. This often occurs when the

newborn are sickly, as these were presumed to be. The dose was finally reduced to 1 Junkman unit per day, since 3 units were also quite intolerable. The final dose of 1 Junkman unit per day was rather ineffectual. Thus the time and dose relations for the very potent thyrotrophic hormone may well be improved. At the dose levels finally chosen for the three substances all pregnant mice delivered normally.

The dose of radioiodine used (100 μc. I^{131}) in a single injection had been demonstrated[53, 54] to be well within the tolerance range, although adult mice receiving this injection might be expected to develop pituitary tumors by 15 months of age. Nevertheless, this dose to the pregnant mouse was sufficient to reduce by some 20 to 25 per cent the length of the thyroid lobes, with the accompanying radionecrosis. It is probable that a higher dose might have overcome any protective value of the antithyroid drugs against the damage by subsequently injected radioiodine, and that the effect of a lower dose might have been beyond determination.

These studies substantiated the earlier ones relative to the rapid rate of radioiodine excretion as evaluated by Geiger-Müller counter determinations. That thiouracil and methimazole facilitated or hastened radioiodine excretion was proved, since the hormone-treated pregnant mice lost more iodine than did even the nonpregnant controls. Pregnancy normally decreases the excretion rate due possibly to the related enlargement of the thyroid gland.[19] Put another way, the presence of fetuses with functional thyroids may aid in radioiodine retention.[53, 54]

We come now to the matter of distribution of radioiodine, and the thyroid protective influences, between the mother and her offspring. As shown in Table II it appears that in addition to aiding radioiodine excretion, the thiouracil treatment also partitions the isotope in such a manner that the fetuses get only about 26 per cent of what is retained. In the controls there appeared to be approximately equal distribution of the available radioiodine between the mother and her entire litter.

In examining the data, litter by litter, it is found that the average size of the litters, of the mice exposed both to the thyroid drugs and the radioiodine, was as follows:

Thiouracil	6
Methimazole	8
Controls	9

Thus, those litters exposed to the thiouracil were smaller than the control litters and they showed the lesser retention (per litter) of the radioiodine. However, while there was a size differential of 9/6 between the controls and thiouracil litters, the percentage of radioiodine going to the litters showed a reverse differential of 54/74 per cent. This might suggest that the smaller the litter the less the concentration of substances available through the mother. Entirely by chance, the larger litter average was from the pregnant females chosen to be the controls. This was fortunate if one considers the possibility that litter size might be correlated with litter avidity for the hormones or for the available radioiodine. The average data are shown in Table IV.

The figures in Table IV show the average amount calculated from the average number of offspring under the

different conditions, and give us values for the various treatments which again substantiate the thesis that thiouracil and methimazole pretreatment will afford some protection of the offspring against radioiodine when administered to the pregnant mouse. In fact one might state that the thiouracil-pretreated pregnant mouse will deliver less than half the amount of radioiodine to each of its litter members, as compared with the controls, regardless of litter size. An equally valid assumption would be that the avidity of the thyroids of the mother and her fetuses for radioiodine is altered by this one treatment. Which state obtains will await further investigation. yet Graph I indicates that, in general, similar trends are seen in the maternal thyroid glands. In one instance, namely, methimazole offspring, the thyroids of the offspring were longer and wider than those of the mothers. This, at two months following treatment of the mother, may indicate a more sensitive (i.e., greater) response of the young than of the maternal thyroid to this substance. Nevertheless, or possibly in spite of this fact, the methimazole-treated fetuses were not correspondingly protected against radioiodine necrosis. Thus it is suggested that thiouracil may not cause a persistent hypertrophy of the fetal thyroid, seen after two months, but that

TABLE IV. TWENTIETH DAY

TREATMENT	% I^{131} RETAINED BY LITTER		ABSOLUTE I^{131} RETAINED BY MOTHER + LITTER		ABSOLUTE I^{131} RETAINED BY LITTER	ABSOLUTE I^{131} RETAINED BY EACH OFFSPRING
Thiouracil	26	×	17	=	4.4%	0.73%
Methimazole	33	×	20	=	6.6%	0.83%
Control	46	×	32	=	14.7%	1.63%

The histological study, while not subject to quantitative evaluation, nevertheless tended to support each of the observations made above. There was no doubt that the radioiodine reached the fetuses by way of the placenta, and the major effect was via this channel even though some residual radioiodine may have reached the suckling young through milk after birth. The thyroids of offspring exposed to thiouracil and then radioiodine through the mother, studied two months later, appeared to be very efficiently protected thereby. Methimazole afforded some protection, but 1 Junkman unit per day of thyrotrophic hormone afforded no real protection against the radionecrosis.

The emphasis in this paper has been on the fetal or offspring thyroids and it does cause the young thyroid to be more refractory toward radioiodine adsorption, and absorption of this isotope is a necessary prerequisite to radionecrosis of the thyroid gland.

SUMMARY AND CONCLUSIONS

1. Pregnant mice were treated with various thyroid-affecting compounds (thiouracil, methimazole, and thyrotrophic hormone) for three days and then with radioiodine in order to determine any modification in damage to maternal or fetal thyroids. The study included determination of retained radioactivity at different time intervals as well as accurate measurements of thyroid gland size and a histological analysis at two months.

2. Pretreatment with the larger dose of thyrotrophic hormone caused

the pregnant mouse to *retain* more of the radioiodine while both thiouracil and methimazole caused the pregnant mouse to *excrete* more of the radioiodine than the pregnant controls. The lower dose (1 Junkman unit per day) of the thyrotrophic hormone had essentially no effect.

3. When litters were considered as units, regardless of their size, those from thiouracil-pretreated mothers received a smaller portion of the available radioiodine than was retained by the mother. The ratio was essentially 3 to 1 as compared with 1 to 1 for the control mother when compared with her entire litter. Thus thiouracil definitely protected the fetuses and their thyroids. Methimazole had a similar effect but to a lesser degree. This suggests that the hormones and possibly the radioiodine may be channeled through the maternal to the fetal thyroids, or that the maternal thyroids exert some controlling influence over the avidity of the fetal thyroids for either the thyroid substances or radioiodine. One cannot deny the further possibility that the fetal and maternal thyroids might be differentially sensitive to the drugs used. This is suggested by the fact that the pregnant (untreated) controls distributed the radioiodine equally between mother and fetuses. This warrants further study.

4. The single injection of 100 μc. of NaI^{131} to the pregnant mouse on the eighteenth gestation day is sufficient to reduce the size of the maternal and the fetal thyroids, two months later, by at least 20 per cent. Histologically such thyroids are typically radionecrotic. In order to reach the fetal thyroids the radioiodine must pass through the placenta. The lower (tolerable) dose of thyrotrophic hormone appeared to have little effect on the histological picture of the thyroid at two months, compared with those treated with radioiodine alone.

5. Histologically thiouracil definitely protected both the maternal and the fetal thyroids against radioiodine-induced necrosis. Methimazole was histologically protective but to a lesser degree.

6. It was found that the effects of thiouracil, methimazole, or thyrotrophic hormone were direct but brief and transient, while the necrotic effects of radioiodine were slow to be realized. The drugs were used prior to radioiodine injection and did modify the radiation damage to the thyroids of both the mother and her fetuses. A suggestion for continued study would be the possibility that further "protection" of the thyroids might be achieved by postirradiation injection of thiouracil.

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ORAL AND INTRAMUSCULAR CHLOROMYCETIN IN PEDIATRIC PRACTICE

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CHLOROMYCETIN is the broad spectrum antibiotic originally isolated from a soil streptomyces in Dr. Burkholder's laboratory and developed in the Research Laboratories of Parke, Davis and Company. A very extensive number of clinical and experimental studies, now well over 2,000,[1] have appeared in the medical and allied literature attesting to its value in the treatment of a wide variety of infectious diseases. The drug has been administered in a variety of dosage forms, including ointment, capsule, drops (local use), Chloromycetin Palmitate for oral use and solution and microsuspension for parenteral use. The purpose of this paper is to present further clinical and laboratory evidence of the value of oral Chloromycetin Palmitate Pediatric and injectable Chloromycetin in the treatment of many common infectious diseases of infants and children.

The first part of our investigation consisted of laboratory studies, carried out to determine the range of blood levels of chloramphenicol following test doses by both oral and parenteral routes. The level of the antibiotic in the blood may be assayed by a chemical or biological method. The former gives higher results than the latter.[2] Our blood levels were determined by the biological method according to the tube dilution method using twofold serial dilutions as described by C. R. Falk,* with *Klebsiella pneumoniae* PC 1-602 as the organism for the indicator culture.[3]

The second part of our investigation consisted of clinical studies carried out to evaluate the effects of chloramphenicol on the common infections of infancy and childhood. Chloromycetin Palmitate by mouth and chloramphenicol solution and suspension by intramuscular injection were the preparations used.

LABORATORY STUDIES

Procedure.—

1. Chloromycetin Palmitate was administered to thirty-three children. These children had received no other medication for at least five days prior to the study and were either convalescing or had noninfectious diseases. The test dose was administered on waking, and all children were in a fasting state. The medication was measured in a graduate cylinder to ensure accuracy, and the children were weighed on the day of the test. Patients were tested with single doses of 15 and 20 mg. of Chloromycetin Palmitate per kilogram of body weight and with doses of 15 and 20 mg. per kilogram repeated four hours after the

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*Antibiotic levels were performed by Mrs. Ira Rosenthal and Miss Carolyn R. Falk, F.A.P.H.A.

first dose. Blood samples for antibiotic levels were drawn at 2, 4, and 8 hours after the administration of the test dose.

2. Chloramphenicol solution was administered intramuscularly in a dose of 50 mg. per kilogram under the same circumstances as described above. Blood samples for antibiotic levels were drawn at 12-, 24-, and 48-hour intervals after the injection.

Results.—

1. Blood levels of chloramphenicol following oral doses of Chloromycetin Palmitate may be seen in Tables I to III. Adequate therapeutic levels[4] are obtained in two hours in all instances and are maintained for a minimum of eight hours following a single dose. A single oral dose of 15 mg. per kilogram (Table I) was as satisfactory as a single dose of 20 mg. per kilogram (Table II), although higher blood levels persisted until 8 hours with the larger dose. When the 15 mg. per kilogram dose was repeated after 4 hours, blood levels (Table II) were hardly to be distinguished from those following a single dose. Similarly, a second dose of 20 mg. per kilogram 4 hours after the first dose did not increase the subsequent blood levels (Table III) beyond those obtained by a single dose.

2. Blood levels of chloramphenicol following intramuscular injection of a 25 per cent solution of the drug in 50 per cent aqueous acetyl dimethylamine

TABLE I. SERUM LEVEL CONCENTRATIONS—CHLOROMYCETIN PALMITATE (15 MG. PER KILOGRAM)

NAME	WEIGHT LB.	WEIGHT OZ.	DOSE MG.	2 HR.	4 HR.	8 HR.
G.	54	0	367.5	2	<1	<1.0
F.	83	6	570.0	2	2	2.0
K.	37	4	255.0	2	2	<1.0
H.	25	14	187.5	2	2	4.0
M.	46	0	312.5	4	2	2.0
S.	34	4	255.0	2	1	0.5
R.	33	0	225.0	2	1	1.0
D.	33	8	232.5	4	2	1.0
C.	23	0	157.5	4	4	1.0
R.	12	2	87.0	2	1	0.5
P.	77	0	525.0	1	1	0.5
S.	17	0	115.5	2	2	2.0

TABLE II. SERUM LEVEL CONCENTRATIONS—CHLOROMYCETIN PALMITATE (20 MG. PER KILOGRAM)

NAME	WEIGHT LB.	DOSE MG.	2 HR.	4 HR.	8 HR.
R.	33⅛	331	3	1	1
P.	59½	595	1	1	2
C.	21¾	217	2	1	1
D.	19¾	197	1	2	1
D.	30	300	3	2	1
G.	28	280	3	2	1
G.	88¾	887	2	2	1
P.	40½	405	3	1	2
T.	17½	175	1	1	1

TABLE III. SERUM LEVEL CONCENTRATIONS—CHLOROMYCETIN PALMITATE

NAME	WEIGHT LB.	WEIGHT OZ.	SINGLE DOSE* MG.	2 HR.	4 HR.	8 HR.
			15 mg./kg. 2 Doses			
C.	54	2	369.0	4.0	2.0	0.5
D.	20	10	141.0	2.0	1.0	0.5
B.	19	14	135.0	4.0	2.0	1.0
R.	37	4	250.0	2.0	1.0	1.0
S.	36	3	245.0	2.0	1.0	0.5
C.	25	0	171.0	2.0	1.0	0.5
			20 mg./kg. 2 Doses			
R.	55	4	500.0	4.0	4.0	1.0
M.	9	6	85.2	0.5	0.5	0.5
R.	16		146.0	1.0	1.0	0.5
G.	45		410.0	2.0	2.0	0.5
J.	50		454.0	4.0	4.0	1.0
F.	59	8	540.0	4.0	2.0	0.5

Doses given at 3 A.M. and 7 A.M.; levels obtained at 9, 11, and 3.

*Total dosage is two times above single dose.

TABLE IV. SERUM LEVEL CONCENTRATIONS—CHLOROMYCETIN AQUEOUS SUSPENSION (I.M.) (50 MG. PER KILOGRAM)

NAME	DOSE	12 HR.	24 HR.	48 HR.
N. H.	600 mg.	2.0	1.0	1.0
J. R.	500 mg.	2.0	2.0	2.0
W. N.	1 Gm.	4.0	4.0	2.0
R. A.	500 mg.	4.0	<1.0	1.0
J. M.	500 mg.	4.0	2.0	1.0
H. M.	750 mg.	1.0	2.0	1.0

in a single dose of 50 mg. per kilogram remained in the therapeutic range of most pathogenic organisms[4] for a minimum of 48 hours (Table IV).

CLINICAL STUDIES

Material.—A total of 277 infants and children were treated. They varied in age from 1 week to 11 years.

Chloromycetin Palmitate was administered to 151 patients (Group A). This preparation is a palatable ester of chloramphenicol in which the terminal hydroxyl group of the propanediol side chain has been replaced with palmitic acid. This preparation is hydrolyzed in the small intestine and the free alcohol form released for absorption.[5] One teaspoonful (4.0 c.c.) contains 125 mg. of chloramphenicol.

The remaining 126 patients were treated with injectable chloramphenicol intramuscularly. Two preparations were used, a 25 per cent *solution* in 50 per cent aqueous acetyl dimethylamine which may be safely used by intramuscular or intravenous route[6, 7] and a microcrystalline powder which was *suspended* in distilled water or saline. Most of the patients received the solution, given intramuscularly, every 6 hours.

One group received the suspension intramuscularly, given once a day. Dosage in all cases approximated 50 mg. per kilogram per 24 hours and was continued until a satisfactory clinical response was obtained or until it was obvious that the infection was resistant to the drug.

Because it had been suggested, on the basis of in vitro studies,[8] that there is an antagonism between chloramphenicol and penicillin, the group treated by the intramuscular route was divided into two groups. One group was treated with chloramphenicol alone (Group B_1) and one group received simultaneously chloramphenicol and full therapeutic doses of parenteral penicillin.

RESULTS

Chloromycetin Palmitate was used to treat 151 acutely and/or chronically ill patients. The drug was administered by spoon in all except very young infants, in whom a medicine dropper was used. There was no need to disguise the medication in milk or food as it was readily accepted. These were all private patients of one of us (V. L.). They represent a wide variety of infectious diseases of infants and children (Table V). A satisfactory response was obtained in 140 and no response in 11. Of the latter group which did not respond, the diseases in 5 (roseola infantum, measles, "la grippe") have no known effective therapy. Therefore, of the known treatable infections, a satisfactory response was obtained in 135 out of 146, a total of 92 per cent.

The group which was treated with injectable chloramphenicol (Tables VI and VII) numbered 126. All patients were hospitalized, either in the Wyckoff Heights Hospital of Brooklyn, or in Gouverneur Hospital, New York. In general, these patients were more severely ill than those treated with oral medication. Seventy-one received injectable chloramphenicol alone (Table VI) and 55 patients received chloramphenicol and penicillin intramuscularly by separate injection (Table VII).

Tables VI and VII show that the effects of chloramphenicol alone were as satisfactory as the combination of chloramphenicol and penicillin and

TABLE V. CHLOROMYCETIN PALMITATE THERAPY

ENTITY RESP. INF.	AGE RANGE	NO. PATIENTS	DOSAGE RANGE	DAYS TREATMENT	PATIENT'S RESULTS		
					SUBSIDED PROMPTLY	IMPROVEMENT	NO IMPROVEMENT*
Bronchopneumonia	9 mo.-7 yr.	8	4-8 c.c. × 4 i.d.	3-4	8		1 (1) (3) and (4)
Acute tracheobronchitis	9 mo.-6 yr.	11	3-6 c.c. × 2-4 i.d.	2-3	10		1 (1) (2) and (3)
Acute bronchitis	3 wks.-8 yr.	18	2-8 c.c. × 4 i.d.	2-4	17		1 (subsided with penicillin)
Acute tonsillitis†	6 mo.-7 yr.	54	3-8 c.c. × 4 i.d.	2-3	54		3 (2 subsided with penicillin)
Purulent otitis media	6 mo.-7 yr.	11	3 c.c. × 4 i.d.	2-3	9		2 (subsided with penicillin)
Acute ethmoid sinusitis	6 yr.	1	8 c.c. × 4 i.d.	4	1		
Pertussis	6 mo.-3 yr.	5	4-8 c.c. × 4 i.d.	3-5		5 (Cough dimin. rapidly)	
Scarlet fever	7 yr.	1	6 c.c. × 4 i.d.	4		1 (1) (2) (3) and (4)	
Roseola infantum	9 mo.-1 yr.	2	3 c.c. × 4 i.d.				2
"La grippe"	6 yr.	1	6 c.c. × 4 i.d.	3			1
Measles	2-6 yr.	2	4 c.c. × 4 i.d.	3			2
Acute pyelitis	4-11 yr.	7	4-6 c.c. × 4-5 i.d.	3-5	6		1 (resistance to *B. prot.*)
Chronic pyelitis	9-11 yr.	2	6-8 c.c.	5-14	2		
Enteritis (4 da.-1 mo.)	2 wk.-3 yr.	14	2-4 c.c. × 5 i.d.	3-7	14		
Purulent vaginitis (2 wk.)	8 yr.	1	6 c.c. × 5 i.d.	3	1		
Ulcerative stomatitis	6 yr.	1	6 c.c. × 4 i.d.	2	1		
Purulent conjunctivitis	6 mo.-6 yr.	3	2-6 c.c. × 4 i.d.	2-3	3		
Impetigo neonatorum	2 wk.-1 mo.	6	2-4 c.c. × 3-5 i.d.	2-4	6	3 (1)	
Impetigo	7 mo.	1	8 c.c. × 4 i.d.	2	1		
Multiple furunculosis	2 wk.-6 mo.	2	2-4 c.c. × 4 i.d.	4-5	1		1 (response to penicillin)

*(1) Resistant to penicillin.
(2) Resistant to sulfonamides.
(3) Resistant to Terramycin.
(4) Resistant to streptomycin.

†9 with cervical lymphadenitis and 2 with otitis media.

that there was no detectable interference clinically by one drug with the other.

The group treated with injectable chloramphenicol alone responded with rapid cure in 63 out of 71 instances (88 per cent). Of the patients who failed to respond, 4 had diseases which are not amenable to this drug—amebiasis, infantile eczema, primary pulmonary tuberculosis, and acute poliomyelitis. Excluding these cases, the rate of rapid cure was 63 out of 67 (94 per cent).

The group treated with injectable chloramphenicol and penicillin responded with rapid cure in 51 out of 55 instances (92 per cent).

TABLE VI. I.M. CHLOROMYCETIN SOLUTION ALONE

ENTITY	AGE RANGE	NO. PATIENTS	CHLOROMYCETIN DOSAGE RANGE 50 MG./KG./DAY	RESULTS		
				SUBSIDED PROMPTLY	IMPROVED	NO IMPROVEMENT
Bronchopneumonia	4 mo.-10 yr.	19	0.9 - 5.5 Gm.	17	1	1
Bronchiolitis, acute	2 mo.- 9 yr.	6	0.45- 5.75 Gm.	6		
Tonsillitis, acute	6 mo.- 7 yr.	25	0.9 - 5.6 Gm.	25		
Otitis media, acute purulent	1 mo.-10 yr.	3	1.0 -11.0 Gm.	2		1
Adenitis, acute	9 mo. and 2 yr.	2	7.5 - 9 Gm.	2		
Gastroenteritis, acute	3 mo.- 4 yr.	7	1.5 - 5.6 Gm.	4		3*
Abscess	11 da.- 1 yr.	2	0.5 - 1.5 Gm.	2		
Eczema	3 mo.	1	2.7 Gm.			1
Tuberculosis, primary pulmonary	8 mo.	1	5 Gm.			1
Poliomyelitis	4 yr.	1	9.5 Gm.			1
Peritonitis	3 yr.	1	9.0 Gm.	1		
Third degree burn with infection	1 yr.	1	2 Gm.	1		
Pyoderma	7 yr.	1	7.5 Gm.	1		
Pyelitis	1 yr.	1	5 Gm.	1		

*2 patients poisoned.

TABLE VII. I.M. CHLOROMYCETIN WITH PENICILLIN

ENTITY	AGE RANGE	NO. PATIENTS	CHLOROMYCETIN DOSAGE RANGE 50 MG./KG./DAY	RESULTS		
				SUBSIDED PROMPTLY	IMPROVED	NO IMPROVEMENT
Bronchopneumonia	1 mo.-7 yr.	18	0.1 Gm.-10 Gm.	16*		2
Bronchiolitis, acute	1 mo.-11 yr.	4	0.9-2 Gm.	4		
Bronchitis, acute	8 mo.-4 yr.	2	1.6-2 Gm.	1		1
Tonsillitis, acute	3 mo.-7 yr.	24	0.6-6 Gm.	24		
Abscess	18 mo. and 6 yr.	2	1 Gm.-4.9 Gm.	2		
Meningitis infl. and meningitis	4 mo. and 10 mo.	2	4.75-6.25 Gm.	2*		
Roseola infantum	2 yr.	1	3.0 Gm.			1
Furunculosis	3 mo.	1	0.9 Gm.	1		
Cellulitis	1 wk.	1	2.4 Gm.	1		

*3 patients with indurated buttocks.

DISCUSSION

In the investigation of a drug, it is desirable to treat only alternate cases with the drug and to use the remaining

cases as controls by giving them no therapy or placebos. However, this procedure is difficult to follow when dealing with acutely ill patients for whom other known effective therapy is available. Controls are possible only to the extent that some of the patients have already failed to respond to other potent drugs or have remained acutely ill when given only symptomatic therapy. It is recognized that a great many of our patients had self-limited infections and would have recovered eventually with symptomatic treatment. This is true of most infections of childhood, but the reduced period of illness, prevention of complications and of mortality with chemotherapy or antibiotic therapy justify the widespread use of these agents. In the same way it is possible to evaluate an antibiotic, by the more rapid recovery, decreased or absent complications, and reduced mortality in treated patients as compared to untreated cases.

The older textbooks of pediatrics record mortality statistics for hospitalized patients with bronchopneumonia of 10 to 65 per cent with a high incidence of complications.[9] Mastoiditis has followed acute otitis media in 10 to 30 per cent of cases.[10] Acute tonsillitis would last four to seven days, and there was a frequent complication of otitis. Mortality from acute gastroenteritis varied from 20 to 60 per cent.[11] In our series of 277 patients there were 3 deaths; 2 of 20 infants with gastroenteritis died, in both of whom there was a strong suspicion of ingestion of poison, and 1 infant out of 45 with bronchopneumonia died, 10 and 2.2 per cent, respectively, for these diseases.

A patient was considered to have a satisfactory response if the temperature returned to normal within forty-eight hours after the start of therapy and if the patient appeared clinically well. In most of our cases, temperature had returned to normal or was decreasing rapidly twelve to twenty-four hours after onset of therapy. No complications of infection developed in any of our patients after they had started on therapy.

No toxic symptoms developed in the patients receiving Chloromycetin Palmitate. Vomiting and diarrhea were practically unknown. Induration of the buttocks developed in four patients receiving intramuscular chloramphenicol and one infant developed a small area of slough. Blood dyscrasias following Chloromycetin have been described in a number of publications and led to special survey by a Committee appointed by the National Research Council[12] who declared that chloramphenicol may in certain susceptible individuals cause blood dyscrasia. Of the total of 539 case records studied in this regard, 55 recorded the use of chloramphenicol as the only therapeutic agent, with 23 deaths, while 143 patients with blood dyscrasia received chloramphenicol and other drugs and 341 patients with blood dyscrasia received only *other drugs*, chemicals, or radiations, including other broad spectrum antibiotics, or were classified as idiopathic. In our series, no evidence of blood dyscrasia developed. Four patients, not included with our other cases, received Chloromycetin Palmitate twice daily, in doses of 10 mg. per kilogram per day for six to nine months continuously as necessary prophylaxis of severe pulmonary infections. A patient undergoing repeated surgery on the urinary tract also received similar long-

term therapy. No evidence of blood dyscrasia developed in these during therapy or in the eighteen months since the therapy was discontinued.

Alexander[13] and others have pointed out the lack of evidence of cause and relationship of Chloromycetin medication and hemopathology. Mortality statistics fail to show a greater incidence of aplastic anemia in the millions of Chloromycetin-treated patients than is known to occur in equal numbers of the general population.

SUMMARY

Chloramphenicol has been used as the therapeutic agent in a wide variety of acute and chronic infections in 277 children. A satisfactory response was obtained with oral Chloromycetin Palmitate in 135 of 146 treatable patients (92 per cent), with injectable chloramphenicol alone in 63 out of 67 treatable patients (94 per cent), with injectable chloramphenicol and penicillin in 51 out of 55 treatable patients (92 per cent). The intramuscular suspension compares favorably with the ampule solution and has the advantage of needing one injection daily at maximum. No interference between chloramphenicol and penicillin was noted. Gastrointestinal symptoms were almost nonexistent. No blood dyscrasia developed in any of our patients.

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TREATMENT OF PURULENT MENINGITIS WITH TERRAMYCIN (OXYTETRACYCLINE) AND SULFADIAZINE

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RECENT reports[1-11] have indicated that there is a variety of successful therapeutic regimes for the management of specific types of purulent meningitis. Since the early administration of antibiotics in the home to suspected meningitis patients has made recovery of the offending organism difficult after hospitalization, the hospital physician must frequently begin therapy before determining the etiological agent and may never learn the exact cause of the purulent meningitis.

Since the majority of purulent meningitis in infants and children is due to either meningococcus or *hemophilus influenzae*, therapy must be directed primarily at these two organisms. Because of the in vitro efficacy of Terramycin against these organisms,[11-13] a study was undertaken to evaluate this drug in combination with sulfadiazine in purulent meningitis.

The purpose of this paper is to report the results of such a study.

METHOD OF STUDY

Patients.—All patients were those from the pediatric service of King County Hospital. The ages were between 3 months and 10 years.

Signs and Symptoms.—The initial complaints and physical signs were those of classical meningitis in varying degrees of severity. Only one patient demonstrated the typical Waterhouse-Friderichsen syndrome.

Diagnosis.—The diagnosis depended upon recovering purulent spinal fluid. The organism was identified by smear and culture when possible. The cultures were done at the bedside on chocolate blood agar slants. The organisms were identified morphologically and the *H. influenzae* was confirmed by quellung reaction with type B antiserum.

Therapy.—The therapy used in all cases was sulfadiazine and Terramycin.* The sulfadiazine was given in a dose of 200 mg. per kilogram of body weight daily for ten days. The initial doses were given either intravenously or intramuscularly as the sodium salt in a 5 per cent solution at six-hour intervals until oral medication could be retained. The Terramycin was given in a dose of 100 mg. per kilogram of body weight daily. Until oral medication was tolerated, it was given intravenously in an 0.1 per cent solution of glucose and saline or glucose and water. Supportive therapy in-

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*Terramycin was kindly supplied for this study by Chas. Pfizer & Co., Inc., Brooklyn, N. Y.

TABLE

CASE	AGE	ONSET (HR.)	SPINAL FLUID					BLOOD WBC
			CELLS	PROT. (MG. %)	SUGAR (MG. %)	SMEAR	CULTURE	
1	11 mo.	24	10,000	200	19	Influenzae	Influenzae	27,800
2	24 mo.	48	5,000	—	10	Neg.	Influenzae	28,500
3	12 mo.	168	1,900	125	19	Influenzae	Influenzae	32,950
4	15 mo.	72	2,800	100	11	Influenzae	Influenzae	11,400
5	18 mo.	120	860	27	10	Influenzae	Influenzae	14,300
6	24 mo.	48	2,000	71	47	Influenzae	Influenzae	7,700
7	3 da.	48	5,000	100	35	Influenzae	Influenzae	4,800
8	4 yr.	24	18,700	580	10	Influenzae	Influenzae	19,000
9	4 yr.	48	4,300	160	8.6	Influenzae	Influenzae	—
10	18 mo.	48	3,400	250	10	Meningo.	Meningo.	19,600
11	3 mo.	48	1,100	350	69	Meningo.	Meningo.	4,960
12	7 yr.	72	10,600	110	15	Meningo.	Meningo.	16,500
13	12 mo.	144	3,400	53	46	Neg.	Meningo.	18,500
14	5 mo.	72	2,218	88	56	Neg.	Meningo.	21,100
15	30 mo.	48	42,000	320	16	Meningo.	Meningo.	42,000
16	9 mo.	48	6,200	160	58	Neg.	Meningo.	11,000
17	7 hr.	24	22,000	280	60	Neg.	Meningo.	26,450
18	12 mo.	24	4,500	450	10	Meningo.	Meningo.	14,000
19	12 mo.	18	3,808	180	9.5	Meningo.	Meningo.	37,000
20	13 mo.	24	5,950	200	69	Meningo.	Meningo.	26,100
21	6 yr.	36	4,800	270	16	Meningo.	Meningo.	8,200
22	24 mo.	24	13,000	140	50	Meningo.	Meningo.	12,600
23	24 mo.	18	8	—	—	Meningo.	Meningo.	26,000
24	10 yr.	48	1,620	50	40	Neg.	Neg.	22,650
25	6 yr.	48	220	37	42	Neg.	Neg.	6,800
26	11 mo.	48	15,000	500	25	Neg.	Neg.	32,200
27	6 yr.	48	1,300	30	50	Neg.	Neg.	25,900
28	4 yr.	48	7,990	300	10	Neg.	Neg.	20,200
29	4 mo.	48	750	170	90	Neg.	Neg.	18,800
30	12 mo.	24	10,000	280	69	Neg.	Neg.	4,600
31	5 yr.	24	30,000	400	10	?	Neg.	16,100

cluding oxygen, fluids, transfusions, and sedation was given as indicated.

RESULTS

The results of this therapeutic regime are summarized in Table I. There was a total of thirty-one patients so treated. The ages of the patients and the types of meningitis encountered are not unusual and are representative of those seen on the average pediatric service. In most instances, the patients were admitted soon after the onset of symptoms, the longest period being 168 hours and the shortest, eighteen hours. This still permitted many of these patients time enough to secure medication prior to admission, the kind and amount of which could not always be determined, but was most commonly penicillin. This decreased the possibility of isolating the organism and may have influenced the outcome.

The spinal fluid findings were all those of purulent meningitis, demonstrating a predominance of polymorphonuclear leukocytes. No suspected encephalitides have been included in the series. In most instances the

BLOOD CULTURE	STERILE CSF (HR.)	FEBRILE DAYS	HOSP. DAYS	PREVIOUS THERAPY TYPE	PREVIOUS THERAPY TIME*	COMPLICATIONS	OUTCOME
Influenzae	36	7	17	None	—	None	Recovered
Neg.	24	4	12	Pen. Terra.	24 hr.	None	Recovered
Influenzae	24	4	19	?	—	None	Recovered
Influenzae	24	10	26	None	—	Subdural effusion	Recovered
Neg.	24	5	14	Pen. SDZ	72 hr.	None	Recovered
Neg.	24	7	11	Pen.	24 hr.	None	Recovered
Influenzae	24	4	47	None	—	Subdural effusion	Recovered
Neg.	24	3	12	Pen.	6 hr.	None	Recovered
Influenzae	12	—	12 hr.	Pen.	2 hr.		Died
Neg.	24	3	12	None	—	None	Recovered
Meningo.	24	5	23	None	—	None	Recovered
Neg.	24	8	13	None	—	None	Recovered
Not done	24	2	9	Pen.	6 da.	None	Recovered
Not done	24	2	6	Pen.	3 da.	None	Recovered
Neg.	24	13	51	None	—	? Subdural effusion	Recovered
Neg.	24	4	12	None	—	None	Recovered
Neg.	24	2	14	Pen.	8 hr.	Abscess of buttocks	Recovered
Meningo.	24	4	12	None	—	None	Recovered
Meningo.	24	3	12	None	—	None	Recovered
Meningo.	24	3	12	Pen.	24 hr.	None	Recovered
Neg.	24	6	12	None	—	None	Recovered
Neg.	24	6	12	None	—	None	Recovered
Meningo.	—	—	6 hr.	None	—		Died
Neg.	—	2	13	Pen. SDZ	24 hr.	None	Recovered
Neg.	—	3	12	None	—	None	Recovered
Neg.	—	6	17	None	—	None	Recovered
Neg.	—	11	15	Chlor. Pen.	24 hr. 12 hr.	None	Recovered
Neg.	—	5	12	Pen.	12 hr.	None	Recovered
Neg.	—	2	14	None	—	None	Recovered
Neg.	—	5	13	None	—	None	Recovered
Neg.	—	6	14	None	—	None	Recovered

*Prior to hospitalization.

smear and culture revealed the etiological agent. Despite diligent efforts no etiological diagnosis could be made in eight patients. Of these, three had petechiae, suggesting meningococcal infection.

The rapidity with which spinal fluid cultures became negative was determined by daily lumbar taps. In twenty patients the cultures were negative by the second day. In one patient (Case 1) no culture was made until thirty-six hours after admission, and no growth was obtained at that time. In the two patients who died, the culture of one (Case 9) was still positive at twelve hours and no repeat culture was performed on the other (Case 23).

Two patients with *Hemophilus influenzae* meningitis developed subdural effusions. Both patients had persistent fever and vomiting which cleared following the aspiration of fluid. In one patient (Case 7) *H. influenzae* was cultured from the fluid obtained on aspiration of the subdural space. Lumbar fluid cultures

done at the same time were sterile. Streptomycin was added to this patient's therapeutic regime and convalescence was uneventful. One patient who had meningococcal infection failed to respond satisfactorily and subdural taps were considered. The symptoms subsided following a pneumoencephalogram. One patient developed a sterile abscess of the buttocks following sulfadiazine injection. There were two deaths in the series. One was a severely ill patient who demonstrated the Waterhouse-Friderichsen syndrome and died six hours after admission. The second was a 2-year-old boy who was progressing satisfactorily but suddenly developed respiratory distress following a lumbar puncture and died. Autopsy showed herniation of the cerebellar tonsils.

The response to therapy was satisfactory in most patients. The acute neurological symptoms subsided promptly, oral feedings and medication could nearly always be given after twenty-four hours, and the fever returned to normal rapidly. The febrile period recorded refers to rectal temperature of 100° F. or greater. The average period was five days. This is somewhat confused by intercurrent respiratory infection contracted frequently during convalescence.

DISCUSSION

Many effective regimes are available for the treatment of purulent meningitis when the etiological agent can be identified.[1] With the wide use of partially effective agents prior to admission to the hospital, the therapeutist can become confused because of the inability to recover an organism.

Chloromycetin[2-5] alone and with sulfadiazine has been shown to be very effective in the treatment of *H. influenzae meningitis*, but toxicity has been reported with its use.[14, 15] Aureomycin has been reported to be effective by several studies.[6-8] However, a report by McKay, Cook, and Davies[16] suggested that it was not the drug of choice. Terramycin has been shown to be effective in vitro against both *H. influenzae*[12, 13] and meningococcus,[11] and Hoyne and Riff[9] have treated twenty-seven patients with purulent meningitis by sulfadiazine and Terramycin with one fatality. Of these, fourteen were due to meningococcus, six to *H. influenzae*, and seven to pneumococcus. The one death was due to a pneumococcal meningitis.

The over-all results using Terramycin and sulfadiazine therapy in this group compare satisfactorily with other series reported with Aureomycin and Chloromycetin. Despite the reported[13] lack of penetration of Terramycin through the meningeal barrier, the spinal fluid cultures were nearly all negative in twenty-four hours. This appears to represent a satisfactory bacteriological response to therapy. In some instances the organisms could still be identified on smear after twenty-four hours, but could not be cultured.

Whether sulfadiazine is necessary was not determined. Since there is no contraindication and there is evidence that it is useful for *H. influenzae*[17] and meningococcus,[10] it was used in all cases. However, the only complication of therapy was a sterile abscess from sulfadiazine.

The probability that the organism in the eight patients in whom no diagnosis could be made was either

meningococcus or *H. influenzae* is suggested in part by the excellent response to therapy. However, since Hoyne and Riff[9] have reported six patients with pneumococcal meningitis successfully treated with Terramycin the possibility exists that some of our undetermined cases may have been pneumococcal meningitis.

The degree to which previous medication interfered with the bacteriological diagnosis and influenced the outcome of the disease cannot be determined. Certainly every effort should be made to establish the exact diagnosis so that specific therapy can then be given. However, since prompt therapy does influence the outcome of meningitis the early administration of one of the wide-range antibiotics would appear more efficacious than penicillin. From the results of this study, Terramycin would appear to be the drug of choice because of its effectiveness, ease of administration, and lack of undesirable side reactions.

SUMMARY

Thirty-one patients with purulent meningitis were treated with Terramycin and sulfadiazine. Of these the causative organism in nine was *H. influenzae*, fourteen were found to have meningococcus, and eight were unclassified. The medication was given parenterally until it could be tolerated orally, usually within twenty-four hours. Therapy was continued for ten days and was well tolerated. One patient developed a sterile abscess due to sulfadiazine. There were two fatalities, one due to meningococcus meningitis exhibiting the fulminating Waterhouse-Friderichsen syndrome and the other due to herniation of the cerebellar tonsils following lumbar puncture. The remaining patients gave evidence of rapid bacteriological and clinical responses. Two patients developed subdural effusions from one of which the organism was recovered in the aspirated fluid although the patient's spinal fluid showed no growth. These over-all results compare favorably with previously reported series using Chloromycetin and Aureomycin.

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ERYTHROMYCIN SUSPENSION IN CHILDREN

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A NEW antibiotic, erythromycin (Ilotycin*), has been reported to have a wide range of antibacterial activity and to be effective clinically.[1, 2, 3, 4] Our purpose is to report the experience with a suspension of this antibiotic intended for pediatric use.

Erythromycin is active chiefly against gram-positive organisms. Clinical reports have demonstrated its effectiveness against pneumococcal pneumonia, streptococcal sore throat, and various staphylococcal infections.[2, 3, 4]

The pediatric preparation used in this study was supplied as cinnamon-flavored granules of the ester, erythromycin ethyl carbonate. Prior to administration, this powder was reconstituted with tap water so that the resulting suspension contained 20 mg. of erythromycin per cubic centimeter. In suspension, it is stable at room temperature for at least two weeks. Erythromycin ethyl carbonate is insoluble and is entirely tasteless whereas erythromycin base has an extremely bitter taste. The administration of this compound to adults results in blood levels quite comparable to blood levels obtained with erythromycin base administered in coated tablets. Unlike erythromycin base, the absorption of the ethyl carbonate is not influenced by the ingestion of food.[4, 5]

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*Erythromycin, Lilly. The drug was supplied by Eli Lilly and Company, Indianapolis, Ind.

METHOD

The patients selected for this study were hospitalized on the pediatric wards and the isolation wards of the Indianapolis General Hospital. Complete blood counts, urinalyses, serologic tests for syphilis, and cephalin flocculation tests were done on all patients as soon as they were admitted to the ward. Blood counts and urinalyses were repeated as indicated by the clinical courses. The cephalin flocculation tests were repeated just before the patient was discharged from the hospital. This test was included as a test for possible liver toxicity of this new drug. A dosage schedule of 5 mg. per pound every six hours was used for all patients in this series.

Nose and throat cultures were done on all patients on admission, and other cultures were done as indicated for the individual case. Erythromycin blood levels were done in three subjects by the method described by Ziegler and McGuire.[6]

Individual cases are outlined in Table I. The results of treatment of a wide variety of bacterial infections were, in general, very good. Responses obtained in the treatment of eight cases of otitis media caused by *Micrococcus pyogenes* and pneumococcus were excellent. Several of these patients had been treated previously unsuccessfully with penicillin-sulfonamide combinations. In Cases 3, 10, 12, and 20 the

TABLE I. PATIENTS TREATED WITH ERYTHROMYCIN ETHYL CARBONATE SUSPENSION

CASE	DIAGNOSIS	CULTURE	ERYTHROMYCIN DOSAGE	PREVIOUS MEDICATION	RESULT
1 9 mo. 20 lb.	Bronchopneumonia	No growth	100 mg. q. 6 h. for 5 days	Penicillin 300,000 U.	Excellent Afebrile from 3rd day
2 4 mo. 15 lb.	Acute bronchiolitis	*Str. viridans* *Staph. albus*	100 mg. q. 8 h. for 6 days	None	Temperature response good Afebrile in 24 hours
3 2 yr. 28 lb.	Otitis media with bilateral draining ears Tonsillitis and pharyngitis	*Staph. albus* *Str. viridans*	100 mg. q. 6 h. for 8 days	None	Excellent Afebrile in 24 hours
4 8 mo. 16 lb. 2 oz.	Infectious bronchitis	No growth	200 mg. stat 100 mg. q. 6 h.for 7 days	Triple sulfa suspension	Temperature normal after 48 hr. Chest clear on 7th day
5 2 mo. 10 lb. 3 oz.	Bronchopneumonia Diarrhea	Nose and throat: *A. aerogenes*, nonhemolytic streptococci Anal: negative	50 mg. q. 6 h. for 5 days	None	Temperature down in 24 hours
6 9 mo. 16 lb. 7¼ oz.	Infectious bronchitis Pharyngitis	Nose and throat: *N. catarrhalis, Staph. albus, H. influenzae*	100 mg. q. 6 h. for 5 days	None	Excellent Temperature down in 24 hours
7 3 mo. 15 lb. 8 oz.	Bronchopneumonia Infectious bronchitis	None	100 mg. q. 6 h. for 6 days	None	Afebrile in 24 hours
8 7 yr. 39 lb.	Lobar pneumonia	Pneumococci *Str. viridans* Blood cultures: negative	200 mg. q. 6 h. for 10 days	None	Spiking temperature of 106° F. for 4 days Erythromycin blood level 2nd day 2.56 μg/c.c.
9 8 mo. 16 lb. 2 oz.	Bronchopneumonia	Pneumococci	100 mg. q. 6 h. for 6 days	None	Good
10 8½ mo. 15 lb. 6 oz.	Bilateral otitis media. Mastoiditis rt. operated	Hemolytic streptococci	75 mg. q. 6 h. for 10 days	None	Good Postoperative, excellent

11 5 mo. 17 lb.	Bilateral otitis media	Pneumococci	100 mg. q. 6 h. for 5 days	None	Good
12 2 yr. 28 lb.	Bilateral purulent otitis media	*Staph. aureus* sensitive to erythromycin, resistant to penicillin	150 mg. q. 6 h. for 6 days	Penicillin, 4 days, sulfa, 4 days	Excellent
13 18 mo. 26 lb.	Pneumonia Pleural effusion	Nose and throat: *Str. viridans* Pleural fluid negative	150 mg. q. 6 h. for 11 days	2 weeks previously penicillin, 1 c.c. x 5 sulfa	Good
14 18 mo. 20 lb.	Bronchopneumonia Otitis media	Nose and throat: *Staph. albus, Str. viridans* Blood culture: negative	100 mg. q. 6 h. for 8 days	None	Slow response Spiking temperature 4 da.
15 1½ yr. 20 lb.	Bronchopneumonia Otitis media	Nonhemolytic strep. Hemolytic strep. Pneumococci	100 mg. q. 6 h. for 6 days	None	Good
16 2 yr. 26 lb.	Bronchopneumonia	*Staph. albus* *Str. viridans*	150 mg. q. 6 h. for 7 days	None	Spiking temperature 2 da. to 106° F.
17 2 yr. 26 lb.	Otitis media Tonsillitis Pharyngitis Bronchopneumonia	Nose and throat: *Staph. aureus, Esch. coli*	150 mg. q. 6 h. for 6 days	Penicillin, 1 c.c.	Good Afebrile in 24 hours
18 8 mo. 13 lb. 8¾ oz.	Diarrhea, infectious Pharyngitis Tonsillitis	Anal: no pathogens Hemolytic strep.	50 mg. q. 6 h. for 5 days	None	Good response
19 4 wk. 7½ lb.	Infectious diarrhea Upper respiratory infection	*Proteus vulgaris* *Staph. albus*	50 mg. q. 6 h. for 5 days	Penicillin Sulfa	Good
20 7½ mo. 24 lb.	Suppurative otitis media	Hemolytic *Staph. aureus*	150 mg. q. 6 h. for 7 days	Sulfa	Good
21 3 yr. 30 lb.	Bronchopneumonia Infectious bronchitis	Pneumococci	150 mg. q. 6 h. for 6 days	Penicillin	Excellent response of fever—105° F. to normal in 36 hours
22 5 mo. 15 lb.	Infectious bronchitis	Predominantly pneumococci Nonhemolytic strep. *N. catarrhalis*	75 mg. q. 6 h. for 6 days	None	Good

TABLE I CONT'D

CASE	DIAGNOSIS	CULTURE	ERYTHROMYCIN DOSAGE	PREVIOUS MEDICATION	RESULT
23 11 mo. 20. lb.	Infectious diarrhea Bronchopneumonia	Anal culture—no growth. Throat: pneumococci, *H. influenzae, N. catarrhalis*	100 mg. q. 6 h. for 6 days	None	Good
24 17 mo. 19 lb.	Otitis media Postcervical lymph node abscess	Nose and throat: pneumococci, *Staph. albus* and *Staph. aureus* Abscess: anaerobic streptococcus	100 mg. q. 6 h. for 7 days	None	Good
25 8 mo. 18 lb.	Bronchopneumonia Postmeasles atelectasis	Nose and throat: *Esch. coli, Staph. albus*	90 mg. q. 6 h. for 5 days	None	Temperature ranged from 100° to 105° F. for 5 days; medication changed to Aureomycin
26 8 mo. 17 lb. 7 oz.	Infectious bronchitis Bronchopneumonia	Nose and throat: pneumococci, few colonies *Staph. albus*	90 mg. q. 6 h. for 6 days	None	Afebrile in 48 hours Results good
27 2 yr. 24 lb.	Bronchopneumonia Otitis media	Nose and throat: scant nonhemolytic staph.	140 mg. q. 6 h. for 5 days	None	Afebrile in less than 24 hours
28 14 mo. 22 lb.	Atopic dermatitis secondary infection Nutritional anemia	None	100 mg. q. 6 h. for 6 days	None	Secondary infection cleared rapidly
29 13 mo. 24 lb.	Otitis media Upper respiratory infection	Nose: *N. catarrhalis* Throat: *N. catarrhalis, Str. viridans, Staph. albus*	120 mg. q. 6 h. for 6 days	Penicillin Sulfa	Temperature 106° F. to normal in 24 hours
30 6 yr. 40 lb.	Acute tonsillitis with adenitis	*Str. viridans* Pneumococci	200 mg. q. 6 h. for 5 days	None	Tonsils receded quickly Temperature normal in 48 hours
31 5 mo. 17½ lb.	Bronchopneumonia	Nose and throat: *Esch. coli* Pneumococci	80 mg. q. 6 h. for 5 days	None	Quick response

organisms isolated were demonstrated to be resistant to penicillin in vitro. The organism isolated in Case 10 was a hemolytic streptococcus. Since this organism was reported to be resistant to penicillin, it may have been that the organism was an enterococcus rather than a group A streptococcus. Six patients with infectious bronchitis responded at least as well clinically as ran an elevated temperature of 100° to 105° F. for five days. Therapy was changed to chlorotetracycline with gradual response. A gram-negative bacillus may have been the etiological agent in this case.

In eleven of the thirty-one cases the organisms isolated probably represented simply the normal nasopharyngeal flora. Cultures in these instances

TABLE II. SERUM CONCENTRATIONS OF ERYTHROMYCIN FOLLOWING A SINGLE DOSE OF ERYTHROMYCIN ETHYL CARBONATE SUSPENSION (5 MG. PER POUND)

CASE	WEIGHT (LB.)	DATE	TIME AFTER DOSE	CONCENTRATION μg/C.C.
1	52	2-13-53	2 hr.	0.64
			4 hr.	0.08
2	41	2-13-53	2 hr.	0.64
			4 hr.	0.16
3	58	2-13-53	2 hr.	0.16
			4 hr.	<0.02

TABLE III. SERUM CONCENTRATIONS OF ERYTHROMYCIN FOLLOWING MULTIPLE DOSES OF ERYTHROMYCIN ETHYL CARBONATE SUSPENSION (5 MG. PER POUND)

CASE	WEIGHT (LB.)	DAY OF TREATMENT	TIME AFTER DOSE	CONCENTRATION μg/C.C.
A	12	8th	2 hr.	1.28
B	20	10th	1 hr.	5.12
			2 hr.	<0.02
C	50	3rd and	1 hr.	0.16
		4th	2 hr.	0.32
			3 hr.	0.08
			4 hr.	0.08
			2 hr.	0.04
D	30	4th	2 hr.	0.16
E	38	7th	1 hr.	0.16
			2 hr.	0.08

might have been expected with penicillin. Five patients with bronchopneumonia, with pneumococci predominant in cultures of secretions collected by throat swabs, responded within twenty-four to forty-eight hours, with a fall in temperature and a subsidence of toxic symptoms. One patient with lobar pneumonia (Case 8) responded more slowly but became afebrile after four days. The erythromycin blood level in Case 8 on the second day was 2.56 μg per. The patient with bronchopneumonia postmeasles infection complicated with atelectasis (Case 25) showed either *Staphylococcus albus*, which is the usual normal organism found in the anterior part of the nasopharynx, or a mixture of organisms including *Streptococcus viridans* or other nonhemolytic streptococci, *Neisseria catarrhalis*, *Hemophilus influenzae*, and *Staphylococcus albus*, of which all are found in the normal pharynx. No doubt, in some of these infections the pathogens responsible were missed, and in some cases filtrable viruses may have been the etiological agents. In respect to their response to treatment, the patients in whom no definite patho-

gen was isolated did as well as the other patients.

Eleven of these patients were complicated by the fact that they had moderately severe nutritional anemias (Cases 4, 9, 10, 13, 14, 15, 16, 18, 25, 27, 28). In Cases 10, 13, 18, 25, and 28 whole blood transfusions were given. Other patients were treated with appropriate vitamins and iron. All of the children except one (Case 25) responded well.

All the patients accepted the erythromycin suspension well, and only one patient vomited. Erythromycin was given to four patients (Cases 5, 10, 19, and 23) who had infectious diarrhea complicated by other infections, and the drug was well tolerated without any adverse effect on the diarrhea. The cephalin flocculation test showed no evidence of liver injury. There were no changes in the blood counts indicative of drug toxicity. Most of the patients gained weight during their period of hospitalization, although some showed an initial slight loss during the acute illness.

Blood levels were done on three patients who received single doses of 5 mg. per pound. The results two and four hours after the drug was given are shown in Table II. In Table III are blood levels on patients receiving multiple doses of erythromycin.

DISCUSSION

In this small series of patients, a new pediatric preparation of erythromycin would appear to be clinically effective. One patient developed mild gastrointestinal side effects which may have been the result of a reaction to the medication but might have been a response to the patient's illness. No other toxic effects were observed. The preparation is palatable and was accepted well by all patients. Blood level determinations obtained in nine subjects indicated that absorption was adequate. The serum concentrations were at least several times the in vitro sensitivities of most gram-positive cocci as reported by several investigators[1, 2, 3, 4] The serum levels fall off rather rapidly, and it might be better to use a four-hour dosage interval instead of the six-hour interval used in this study. If the findings of this preliminary study are borne out by studies of large series of cases, this new suspension of erythromycin ethyl carbonate would appear to have promise in the treatment of the more common respiratory tract infections of infants and young children.

SUMMARY

The use of a cinnamon-flavored suspension of erythromycin ethyl carbonate in the treatment of the thirty-one children with various bacterial infections involving the respiratory tract and middle ear is described. This pediatric preparation was well accepted, showed no toxic side effects, and was highly effective.

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MIRROR MOVEMENTS IN A CASE OF PHENYLPYRUVIC OLIGOPHRENIA

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THE term "mirror movements" is used to designate a condition in which the movement in one extremity is automatically accompanied by a movement of the same type in the opposite extremity. In other words, the original movement produces an exact replica of itself, a mirror image, as it were.

The phenomenon occurs in the upper extremities, the hands and arms, the legs being unaffected in any way. Ford[1] claims that the condition is always present at birth and persists throughout life. However, as the years go by, individuals subject to mirror movements learn to dissociate the movements of their two hands and the condition becomes less noticeable.

In their fully developed form, mirror movements may be accompanied by a certain degree of disability. Thus, in one of the cases reported by Smith[2] the patient was unable even at the age of 23 to climb a ladder, since every time he released a rung with one hand, the other hand immediately followed suit. When he carried a pail of milk, he had to carry it with both hands. Before he could open the barn door, he had to set the milk bucket down, or else the pail would drop. He was considered to be clumsy because things dropped out of his hands very frequently. In most cases, however, these movements apparently do not interfere with the patient's activities to an appreciable extent.

Mirror movements appear to occur only rarely as evidenced by the very meager literature on the subject. The only condition in which they have been reported to appear with any frequency has been in cases of the Klippel-Feil syndrome in which the number of cervical vertebra are diminished and fused in one mass. This syndrome is often accompanied by spina bifida, mental deficiency, or other abnormalities. Bauman[3] reports mirror movements in four out of six cases of the Klippel-Feil syndrome. Because of their frequent appearance in this condition and their rarity in others, Bauman believes that mirror movements should be included in the symptom complex of the Klippel-Feil syndrome. Mirror movements have, however, been observed in patients without Klippel-Feil syndrome.

Mirror movements have been reported in more than one member of a family. Bauman[3] reports the presence of mirror movements in an aunt and in a cousin in one of his cases of Klippel-Feil syndrome, both of whom were below par mentally. Smith[2] observed mirror movements in a 23-year-old father and his 1-year-old child, both

From the Dr. Julian D. Levinson Research Foundation.

of whom were otherwise completely normal, mentally as well as physically. These cases of Smith and Bauman suggest a familial trend in mirror movements.

We recently had the opportunity of observing mirror movements in a case of phenylpyruvic oligophrenia.

CASE HISTORY

G. Z. was a white male 8 years of age, the first of two siblings; the other, also a boy, was normal. The parents were healthy. There was no history of familial disease. Pregnancy and birth were completely normal. The birth weight was 6 pounds 1 ounce. There were no complications during the neonatal period. The child's motor development was rather slow. He held his head up at 4 months of age, sat up at 9 months, crawled at 11 months, and walked at 17 months. Speech development was slow. He started saying words at 2 years of age and sentences at 5 years. The child was not completely toilet trained at 8 years of age. He had measles, which was mild and uncomplicated, at 1½ years of age, and an appendectomy at 6 years of age.

The child was considered normal until about 1 year of age when the delay in walking and talking made the parents suspect something was wrong. It was not until the child was 3 years old that it was definitely established that he was retarded. At that time, he was diagnosed as a case of microcephaly and was regarded as such until the real nature of his condition was discovered.

Fig. 1.—Mirror movements in a case of oligophrenia. When the patient pointed the index finger of the right hand, the left index finger pointed automatically.

The mother stated that when the child was 5 years of age she noticed for the first time that whenever he moved one hand the other hand automatically performed the same movement at the same time.

We examined the patient for the first time when he was 8 years old. We found him to be a well-developed, well-nourished boy. His height was 49½ inches, and his weight was 70 pounds, more than ten pounds above the normal weight for his age. He was alert, well-behaved, and coopera-

tive. Vision and hearing were normal and speech was fair. He answered questions intelligently. His head was small, measuring 18 inches in circumference, 2½ inches less than average for his age. His eyes, ears, nose, and throat showed no abnormalities. His neck was not short. His complexion was fair, hair blond, and eyes blue. The left testicle was undescended. The extremities were normal. Neurological examination showed no abnormality whatever in muscle power, coordination, sensibility, or reflexes. The only abnormality found was the mirror movements of the hands. When the child took hold of an object with the right hand, the left hand showed the same movement. When he squeezed the hand of the examiner with his right hand, his left hand also closed tightly. When he closed the door with one hand, the other hand also performed the motions of grasping, turning, and releasing the knob of the door lock. When he pointed with the index finger of one hand, the index finger of the other hand also extended automatically. Every time one hand performed a voluntary movement, the other hand repeated the same movement involuntarily (Fig. 1).

X-ray examination of the head revealed a symmetrically small skull for a child 8 years of age. X-rays of the spinal column, including the cervical region, showed no abnormalities. X-rays of both wrists and hands did not reveal evidence of osseous or joint abnormality and the bone age was compatible with the chronological age. An electroencephalogram showed 5 to 9 per second activity in all leads with a good deal of 4 per second waves in both occipital areas. During Seconal-induced drowsiness, there were isolated spikes in the left occipital region. The impression was an abnormally slow activity in both occipital areas with isolated spikes in the left occipital.

An intelligence test by the revised Stanford-Binet disclosed an I.Q. of 52.

A test for phenylpyruvic acid in the urine was done by adding 5 per cent ferric chloride to the urine. The reaction was positive on several occasions.

DISCUSSION

The diagnosis of phenylpyruvic oligophrenia is well established. The diagnosis of mirror movements is also clearly established.

Essentially, mirror movements are a form of synkinetic movements, also called accessory or associated movements. These consist of certain involuntary movements which tend to accompany certain voluntary movements. Synkinetic movements exist physiologically as, for example, swinging of the arms during walking. In pathologic conditions, however, new synkinetic movements, which do not exist normally, make their appearance.

Monrad-Krohn[4] classifies the synkinetic movements encountered pathologically into three types:

(1) *Generalized synkinetic movements* which consist of involuntary movements in an extremity which tend to produce the typical attitude of predilection of the extremity. As an example of such a movement may be mentioned the involuntary extension of all joints in a paralyzed lower extremity (extension in all joints being the typical attitude of predilection of the lower extremity) upon voluntary exertion with the nonparalyzed side.

(2) *Coordinated synkinetic movements* which consist of involuntary movements of synergic muscle groups, accompanying a voluntary movement in the same limb. An example of this type of synkinetic movement is the Strümpell phenomenon which consists of an involuntary dorsiflexion and supination of the foot occurring upon voluntary flexion at the knee joint of the same paretic limb.

(3) *Symmetrical synkinetic movements* which consist of involuntary movements of imitation in one extremity accompanying voluntary movements of the extremity on the other side. As an example may be mentioned the involuntary flexion movements of the fingers of a paralyzed hand when the patient squeezes someone's hand with the normal hand.

Synkinetic movements of all three types are encountered in pathological conditions of the pyramidal tracts with hemiplegia as mentioned by Monrad-Krohn,[4] Alpers,[5] Purvis-Stewart,[6] and others. In such cases the various types of synkinetic movements always appear on the hemiplegic side while the voluntary movements which provoke such synkinetic movements may be performed either by the opposite nonparalyzed side, as is the case in the first and third type, or by the same paralyzed side as is the case in the second type. According to Purvis-Stewart, synkinetic movements of the imitative type are observed in the hemiplegic less frequently than the other types of synkinetic movements.

Mirror movements are obviously none other than synkinetic movements of the symmetrical imitative type. However, the term mirror movements should be reserved for those individuals who are otherwise neurologically normal.

In the normal infant there is a tendency for movements of one limb to be accompanied by similar involuntary movements of the opposite limb. According to DeJong,[7] however, such tendency disappears as soon as coordination and muscle power are acquired. These movements may persist to a mild degree in children as "transient mirror movements." If, however, these manifestations persist to any marked degree, they should, according to DeJong, be considered definitely pathologic.

In neurologically intact individuals, and particularly in those with undamaged pyramidal tracts, mirror movements are extremely rare. This accounts for the small number of reports on this subject in the literature. The importance of the present report lies in the fact that in addition to the association of mirror movements with the Klippel-Feil syndrome, and with mental retardation of unspecified nature, it has been shown to exist also in association with phenylpyruvic oligophrenia.

The pathology of mirror movements is still obscure, since no autopsies were ever reported in the literature. Several hypotheses have been suggested. One of these mentioned by Ford[1] postulates a defect of the decussation of the pyramidal tracts. According to this hypothesis, it is assumed that only partial decussation occurs with the result that impulses which should be distributed to only one side of the cervical segment of the spinal cord are actually distributed to both sides. Another hypothesis mentioned by Ford is that both the pyramidal tracts may arise in one hemisphere so that identical stimuli are sent to the muscles on either side of the body. Bauman[3] suggests a developmental defect in the corpus striatum.

Wherever the anatomical site of the lesion in the central nervous system may be, whether in the cortex, in the pyramidal tracts, in the corpus striatum, or elsewhere, it appears that such a lesion may be produced by various causes. Heredity appears to be an important factor as is shown by

the familial incidence in Smith's and Bauman's cases. However, other factors may be responsible for the lesion, such as cerebral hemorrhage. Our case provides a further cause of such damage, namely, phenylalanine which in excessive amounts in the blood may produce not only cortical damage with resultant mental retardation, but apparently also damage to the primary anatomical site which is responsible for the appearance of mirror movements.

It would be interesting to examine a larger number of cases of phenylpyruvic oligophrenia for mirror movements to try and find out whether there is any constant, or at least frequent, association between the two conditions. If any such relationship is found it would further be of interest to find out whether these movements are present from birth, as claimed by Ford,[1] or may make their appearance later in life.

SUMMARY

A case of mirror movements in a patient with phenylpyruvic oligophrenia is reported, and its clinical significance and pathological implications discussed.

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INGUINAL HERNIAS IN INFANTS AND CHILDREN

A Critical Study of 250 Patients Treated by Surgery

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THE problem of hernias in infants and children is different from that of adult patients. Although most of the discussion on inguinal hernias in the literature and textbooks concerns adult patients, the principles governing treatment in these patients cannot be applied to the treatment of inguinal hernias in infants and children.

Inguinal hernia in the child is nearly always of the indirect type and is due to the failure of the processus vaginalis to close properly, and not due to muscular weakness. The muscular and fascial structures forming the inguinal canal are essentially normal and take no part in the formation of a congenital hernia. A repair of these structures is, therefore, not necessary to cure the hernia.

If the entire processus vaginalis remains patent, then the hernia extends down the cord to the tip of the testicle and is known as a complete hernia. If obliteration is partial or interrupted, then an incomplete hernia or hydrocele of the cord or testes will result. Crying and straining cause the appearance of the hernia only if the processus vaginalis did not close properly. The hernia appears most frequently in the early months of life and is most frequently seen on the right side. This is probably due to the fact that the right testicle descends at a later date than the left and the processus vaginalis closes off at a later time.

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The diagnosis of inguinal hernia is not always easy in children and often the hernia cannot be demonstrated. Frequently, the diagnosis of hernia is made because the mother or physician has seen the hernia in the scrotum on previous occasions. It may be especially hard to differentiate an incarcerated hernia from a hydrocele. This is especially true because the hernia in an infant will often transmit light. Torsion of the testicle may also be confused with an incarcerated hernia in a child and must be considered in the differential diagnosis.

The possibility of a spontaneous cure in these patients is rare and almost never occurs after the first few months of life. Since the cause of hernia in children is a patent sac, the basic principle of treatment is a high ligation and excision of the sac. Ferguson[2] in 1899 was one of the first to advise against disturbing the position of the cord in repairing a hernia in infants and children. A few years later several surgeons[3, 6, 8] advised simply making a small incision over the external ring and ligating and excising the sac. More recently Duckett[1] has emphasized this point and usually allows his patients to go home the day after operation. Potts[5] has also emphasized this and does not cut the external ring in exposing the sac.

However, in spite of the good results obtained by this simple treatment, there appear in the literature and textbooks today innumerable articles advising prolonged truss treatment, de-

laying the operation until the child is 2 to 4 years old, injection treatment, and plastic repairs of the muscle and fascial structures.

ANALYSIS OF 250 CASES

This report is based on the study of 250 cases of inguinal hernia in children, from birth to 12 years of age, operated upon in the past five years at the John Gaston Hospital, Memphis, Tenn., the teaching hospital of the University of Tennessee. From Table I it may be seen that only seventeen of these were noted in the female. The hernia was bilateral in ten and associated with cryptorchidism in five. Hydrocele was associated with the hernia in nine cases. The hernia occurred on the right side in 70 per cent of the cases. From Fig. 1 it is apparent that the great majority of these hernias became evident within the first year of life. Eighty-nine of the 250 hernias reviewed were irreducible when admitted to the hospital. Over two-thirds of the patients admitted under one year of age had irreducible hernias, and over two-thirds of all incarcerated hernias were seen before the first year of life. The younger the age of the child in months, the more frequently incarceration occurred. More than three-fourths of the patients under 6 months of age were found to have irreducible hernias at the time

TABLE I

ANALYSIS	NO. OF CASES	PER CENT
Total	250	100
Right	175	70
Left	65	26
Bilateral	10	4
Male	233	93
Female	17	7
Associated hydrocele	9	4
Associated cryptorchidism	5	2

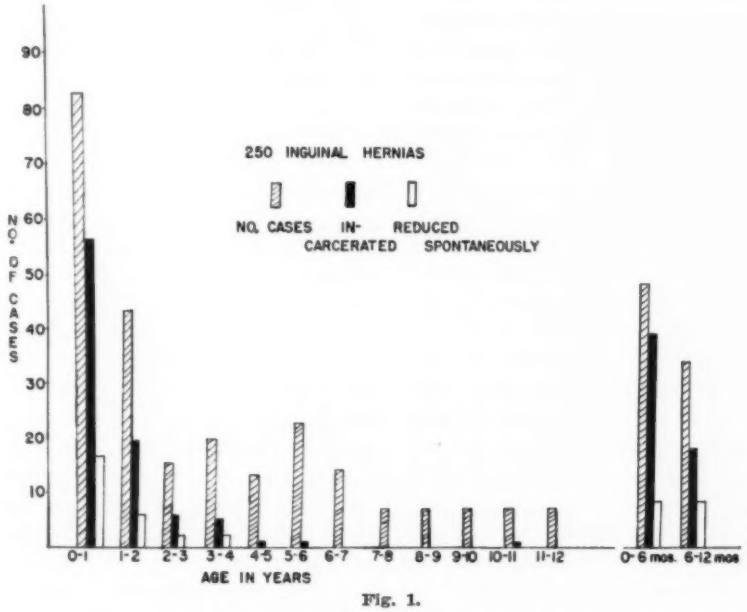

Fig. 1.

of admission to the hospital, and the hernias in all ten patients (or 100 per cent) under one month of age were irreducible on admission to the hospital. Eighty-five per cent of the irreducible hernias occurred before 2 years of age. Incarceration was rarely seen after the fifth year.

Incarcerated hernias in infants are easier to reduce than in adults. Twenty-six of the eighty-nine incarcerated hernias reduced either spontaneously or with mild sedation and elevation of the hips while the patient was on the ward, and another ten spontaneously reduced under anesthesia before the hernia sac could be opened. In none of the eighty-nine cases of incarceration was the bowel gangrenous or resection necessary.

There was one death in the 250 cases. A 2-year-old Negro male with a history of strangulation of six hours' duration was operated upon and the hernia repaired. The hernia reduced under anesthesia, and the bowel was not visualized. The patient did well postoperatively for eight hours then suddenly expired, apparently from aspirating vomitus.

All of these patients were operated upon under drop ether anesthesia, and either the sac was excised with no type of muscular repair or a Ferguson repair was done. In two patients the neck of the sac was tied off with a silk suture but the sac was not divided or excised. A nonabsorbable suture was used in all cases. There were no restrictions of any kind placed on these children in the postoperative period. They were usually put on a regular diet or formula within twenty-four hours. Skin sutures were removed on the fourth to the sixth postoperative day and the patient then discharged.

Thirteen of the 250 patients developed an upper respiratory infection as a postoperative complication with temperatures reaching as high as 103° F. One had an acute otitis media, one had a gastroenteritis, and one had a hematocele of the scrotum that responded to aspiration.

Out of 248 cases that were operated upon where the sac was excised, there were no known recurrences. These cases have been followed for a period of a few months to seven years. However, the two cases that were done by placing the silk ligature around the sac but not dividing it recurred within six months.

COMMENT

The fact that in some cases it may be difficult or impossible to demonstrate a hernia even when the patient is crying or straining has not been emphasized in the past. In nine of the patients who were operated upon, the hernia could not be demonstrated either in the outpatient department or after the child had been admitted to the hospital, the diagnosis being made on the history of the mother's having seen the swelling in the scrotum on a previous occasion. In all nine of these patients a sac was found at operation, and in a few a complete hernia was present. We have also found that transillumination in these children is of little benefit so far as the differential diagnosis is concerned. This was impressed upon us by a 2-year-old child who was admitted to the hospital at night with a swelling in the scrotum of two days' duration. A diagnosis of hydrocele was made because the child did not appear acutely ill and had not vomited, the mass transmitted light, and no peristalsis could be heard

over the mass. However, the next morning the diagnosis was obvious and at operation a strangulated loop of ileum, dark blue in color, was found to be present in the hernia sac.

A hernia sac was found to be present in all patients with hydrocele of the cord who were operated upon, and we feel that a hernia is present in practically all of these cases. If a sac is not obvious, one should open the peritoneal cavity at the point where the processus vaginalis closes off, there being a short protrusion of the peritoneum down the cord in this area.

One of the interesting results noted from this study and not emphasized in the past was the high instance of incarceration and of strangulation that appeared in the early months of life. The younger the patient, the more likely incarceration occurred. From these observations it appears that the question of when to repair the hernia in a child is obvious. Since most of the incarcerations occur in the early months of life, and our study shows 84 per cent occur within the first two years of life, it seems better judgment to repair the hernia at an early age than to wait until the child is older. We believe that age is no contraindication to surgery. Because of the high instance of strangulation in the early months of life these hernias should be repaired when the diagnosis is made, provided the child or infant is otherwise normal and gaining weight. It also appears that the younger the patient the smoother the postoperative course will be.

It was interesting to note, too, that none of the cases of strangulation required resection. One patient, 6 months of age, had a strangulated hernia of four days' duration. The child appeared very ill, almost moribund, with marked dehydration, acidosis, and electrolyte imbalance. We felt sure that this child would have gangrenous intestine. However, after treatment with intravenous fluids and blood to correct electrolyte imbalance, the child improved and was operated upon. At operation it was found that the constricting external ring had cut a loop of jejunum approximately half in two in the transverse diameter. The bowel was viable both proximal and distal to the injury, and the edges were cut so clean that the bowel was closed without débriding the edges. The child made an uneventful recovery and was discharged on the seventh postoperative day. Although we did not see any gangrene of the intestine in our cases, Thorndike and Ferguson[7] reported four cases of gangrene in 106 patients with strangulation. Duckett[1] found none in 380 cases of hernias in children. Larsen[4] reported one in 111, and Potts[5] reported one in 200.

Because of the fact that a number of incarcerated hernias are reducible and because of the low instance of gangrene, we feel that one is justified in making some attempt to reduce the hernia with mild sedation, elevation of the hips but no pressure or manipulation of the hernia. If the hernia is spontaneously reduced, the child is kept in the hospital and the hernia repaired later as an elective procedure. It is useless and may be harmful to attempt to reduce the hernia when a child is crying. If the hernia is not reduced by conservative means in from three to four hours, the patient should be operated upon.

One of the biggest dangers in children with strangulated hernias is the fluid and electrolyte imbalance that

occurs. These children become acutely ill in a short time with dehydration and acidosis, especially when vomiting is present. If this problem is given prompt attention and the fluid and electrolyte imbalance corrected before surgery, the mortality rate will be very low.

TREATMENT

We believe that a truss should be worn only in those poor-risk patients where surgery is contraindicated. Trusses do not cure a patient and are troublesome and unsatisfactory at best. It is hard to see how a truss can obliterate a sac and cure a patient when one can tie off the sac with a silk suture without dividing it and the hernia will recur.

The basic principle of treatment in these cases is a high ligation and excision of the sac. We do not believe that a repair of the musculature of the canal is important or necessary. If one secures a high ligation and an excision of the sac, the patient will be cured. However, in the older child if it is felt that some type of repair is necessary we prefer the Ferguson technique of suturing the conjoined tendon over the cord to the shelving margin of Poupart's ligament with a few sutures. This does not disturb the cord and obviates the possibility of shortening the cord or interfering with the circulation as might occur when it is transplanted or dissected from its bed. It makes very little difference what type of suture material is used. However, we feel that the patient is more comfortable when a nonabsorbable suture is used in the repair. In infants it is unwise to pin a diaper on the patient because this is likely to cause wound contamination.

SUMMARY AND CONCLUSION

1. Hernias in infants and children should be repaired at the age at which they are diagnosed because of the high instance of incarceration in the early months of life.

2. Because some of these hernias can be easily reduced and because of the low instance of gangrene, one is justified in trying to reduce the incarcerated hernia conservatively and in doing an elective repair after correction of any existing electrolyte deficiency.

3. The general condition of an infant with a strangulated hernia may deteriorate rapidly due to fluid imbalance.

4. The essential element in the surgical treatment is a high ligation and excision of the sac.

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CAT-SCRATCH DISEASE

Report of a Case in 1925

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THIS case of cat-scratch disease is reported because of the year (1925) in which it occurred, and the fact that the correct diagnosis was not made until 1953, some twenty-eight years later. Recently a number of cases have been reported from various parts of the United States, and in a recent review the statement is made that Forshay[1] has seen cases in the United States since 1932.

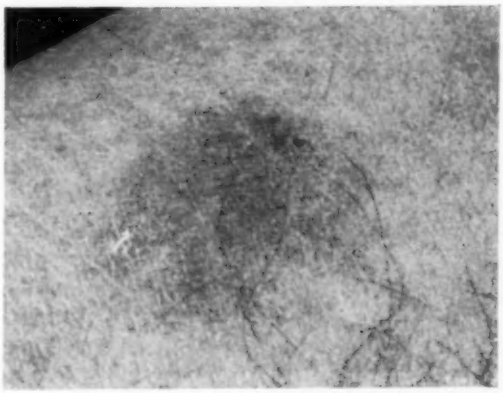

Fig. 1.—Skin reaction at 48 hours. Diameter 2 cm.

CASE REPORT

M. F. R., a physician, aged 35, was admitted to Columbia Hospital on Jan. 19, 1926, with a complaint of tender, swollen glands in the right axilla. Six weeks previously the patient had played with a kitten and had acquired what he called "ringworm infection." His wife had also played with the kitten and had also acquired "ringworm infection." While playing with the kitten, the patient was scratched on his right thenar eminence. Within a few days he developed two blisters and an area of redness and infiltration at the site of the scratch. Two weeks later he developed an enlargement of the glands in the right axilla which later became painful and tender. On January 18 he felt pressure and fluctuation with hard swelling of the right epitrochlear gland. The temperature during this period ranged from 99° to 100° F. The glands were incised, and a mass dissection of the axillary glands was done. The pus was cultured on blood agar, Loeffler's, and many other media. Stained smears of the pus showed no organism. The blood was sent to the National Institutes of Health, Washington, D. C., for further cultures and agglutinations. A report was made that no sporotrichosis was found. The agglutinations were negative for typhoid, paratyphoid, and tularemia. The blood counts were not unusual. Sec-

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tions of the axillary mass showed subacute inflammation with marked hyperemia, marked fibroblastosis, and endothelial proliferation. Two guinea pigs were injected with some of the purulent material. The case was forgotten until January, 1953, when a social discussion brought up the subject. The physician showed his scar and wondered what was the diagnosis. Sections from the guinea pigs' lungs were located in the hospital and sent to Dr. Lee Foshay, Cincinnati. Dr. Foshay kindly reported the following:

"These slides are interesting. They do, indeed look considerably like the cat-scratch disease picture in human nodes. The reticular cell proliferation and accumulations of eosinophils are quite characteristic of C-S-D human nodes at a certain stage of development."

I had just prepared antigen from material aspirated from a case of cat scratch disease at the Milwaukee County General Hospital. Five hundredths of a cubic centimeter of this antigen was injected into the skin of the patient's forearm and a marked reaction was obtained within twenty-four hours. The immediate zone measured 2 cm. The areola measured 5 cm. Fig. 1 shows the skin reaction in forty-eight hours. At the end of three weeks there was still a thickened infiltrated area which measured 1 cm. in diameter and about 0.5 cm. in depth. Fig. 2 illustrates this reaction.

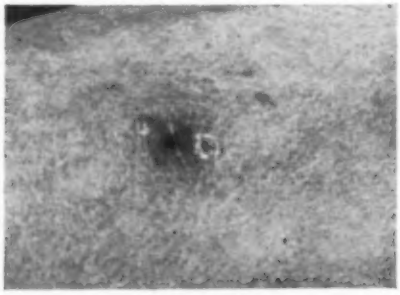

Fig. 2.—Skin reaction three weeks later. Diameter 1 cm.

SUMMARY

A case of cat-scratch disease is presented which apparently occurred in December, 1925. It was recognized and the diagnosis established in 1953. The skin test for cat-scratch disease appears to be specific and diagnostic. Apparently the skin test may remain positive for many years after the disease is acquired.

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ACUTE PULMONARY EDEMA DUE TO NEAR-DROWNING IN FRESH WATER

CASE REPORT

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ACUTE pulmonary edema occurring in conjunction with drowning or near-drowning has apparently been recognized as a clinical entity for some time. Cot[1] in 1931 suggested that aspirated water caused a fulminating pulmonary edema which "drowned" the victim. Case reports have appeared only recently. The literature to date contains a total of twelve published cases involving human beings. Trocmé and Lafarie[2] reported three cases with recovery in 1947. Two of their case reports were accompanied by x-ray evidence of pulmonary edema. The edema was thought to be produced by the presence of water in the respiratory system and by modifications in the permeability of certain parts of the pulmonary tissues. In 1949 Trocmé and Lebert[3] reported two additional cases of near-drowning. Both reports were accompanied by x-rays. Buchtala[4] in 1950 reported six cases of lung edema; two patients died and four recovered. X-ray evidence was presented for five of the six cases. Buchtala thought the edema was centrally conditioned, or centroneurogenic in origin. Romagosa and his co-workers,[5] also in 1950, published a single case report with x-rays of changes that occurred in the lungs during recovery from near-drowning. The changes were ascribed to pulmonary edema.

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CASE REPORT

V. M. S. (MGH No. 15113), a 10-year-old white female, was admitted to the Minneapolis General Hospital at 4:00 P.M. on July 26, 1951. She had been taken from one of the city freshwater lakes after being immersed for an estimated two to three minutes. A spectator applied artificial respiration for a short period of time until the arrival of a rescue squad from the city fire department. She was immediately removed to the Minneapolis General Hospital, meanwhile receiving oxygen by mask. No artificial respirator, or "pullmotor," was used by the rescue squad.

Upon her arrival at the hospital, the patient was disoriented and extremely agitated, crying and thrashing about with "swimming movements" of the extremities. She was hyperventilating. Her skin was dusky, and her mucous membranes and nailbeds were deeply cyanotic. The body temperature was 100.8° F. by rectum, the pulse rate varied from 150 to 160 per minute and was at times thready, the respiratory rate ranged between 60 and 80 per minute, and the blood pressure was 100/60 mm. of Hg. Bloody mucus was present in the pharynx although there was no evidence of injury to the mouth or pharynx. The heart tones were regular and of good quality. A soft systolic murmur was heard at the apex. Breath sounds

were present bilaterally, but many fine, moist râles were heard throughout both lung fields. The physical examination was otherwise negative.

A study of the blood revealed 14.5 Gm. of hemoglobin per 100 c.c. and 22,300 leukocytes per cubic millimeter, of which 90 per cent were neutrophils and 10 per cent lymphocytes. The hematocrit was 44 per cent. The carbon-dioxide combining power was 22.9 meq. per liter. A bedside x-ray of the chest revealed small areas of increased density distributed uniformly throughout both lung fields. The appearance was consistent with the changes seen in pulmonary edema. (Fig. 1.)

she remained in the oxygen tent. The oxygen concentration in the tent was 50 per cent according to the Beckman Oxygen Analyzer. At 10:00 P.M. the patient was started on positive pressure oxygen, 8 liters per minute at 4 cm. of water, for twenty-minute intervals, alternating with oxygen by B.L.B. mask at atmospheric pressure for forty-minute intervals. The oxygen concentration in the B.L.B. mask was 50 per cent according to the Beckman Oxygen Analyzer. Oxygen saturations were estimated at this time with an ear oximeter, using as the base line an arbitrary setting of 98 per cent while the patient was breath-

Fig. 1.

Fig. 2.

Fig. 1.—Bedside film of the chest showing acute pulmonary edema approximately two hours following near-drowning.

Fig. 2.—Bedside film of the chest taken approximately nine hours following near-drowning. Note the increased bilateral pulmonary edema as compared with Fig. 1.

Immediate therapy included oxygen by tent, Trendelenburg position, prophylactic penicillin, and intravenous fluids by very slow drip in order to have a portal for administration of medication in case of shock. Two doses of adrenal cortical extract were given because the patient was thought to be in impending shock. By 8:00 P.M., four hours following admission, the patient was responsive and cooperative. Her skin color was somewhat improved but still dusky even while

ing oxygen by B.L.B. mask. In comparison with this figure, the oximetric reading was 85 per cent while the patient was breathing room air, and 100 per cent while the patient was breathing oxygen under positive pressure. At 1:00 A.M. on the second hospital day, three hours after positive pressure oxygen therapy had been started, the bedside chest x-ray was repeated. It was interpreted as revealing a rather definite increase in the bilateral pulmonary edema. (Fig. 2.) Another

film of the chest at 8:00 A.M. showed some improvement. By this time the patient's general condition had also improved. Her color had become normal and she was able to take oral fluids. The pulse rate had decreased to around 120 per minute, and the respiratory rate to approximately 40 per minute. The blood pressure had remained stable. Fewer râles were heard in the chest. A urinalysis was essentially negative except for a faint trace of albumin. The carbon-dioxide combining power was 27.1 meq. per liter, and the blood chloride was 109 meq.

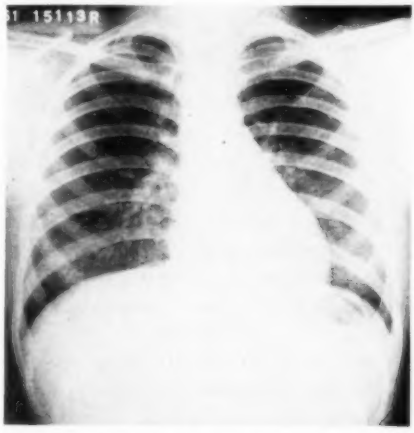

Fig. 3.—Negative chest film taken four days after near-drowning.

per liter. The oxygen by positive pressure was discontinued although oxygen by tent was continued for a few hours longer. Improvement continued during the third hospital day. The pulse rate was 110 to 120 per minute, and the respiratory rate was 36 per minute. A film of the chest showed much less pulmonary edema. By the fourth hospital day the patient was afebrile and feeling well except for an occasional cough. The chest was clear on physical examination. On July 30, the fifth hospital day, a chest x-ray was completely negative. (Fig. 3.) The patient was discharged on the sixth day of hospitalization, completely free of symptoms and physical abnormalities. The pulse rate was 80 per minute, and the respiratory rate 20 per minute. Her vital capacity was 1.6 liters. Just before discharge, the oximeter studies were repeated. A base line of 109 per cent was established while the patient was breathing room air. The oximeter reading was 104 per cent after the patient had exercised for four minutes, and 110 per cent after she had breathed oxygen by mask while resting for four minutes.

The patient had no further difficulties. In a letter written on May 27, 1953, her mother stated that she was in excellent health.

DISCUSSION

Although the etiology of the pulmonary edema that occurs in conjunction with drowning or near-drowning has not been established, several experimental studies suggest that its genesis is in accord with classical concepts of edema formation.

Pulmonary edema, in general, is caused by two basic mechanisms. One mechanism is an excess of capillary hydrostatic pressure over colloid osmotic pressure. Examples of this are left-heart failure, obstructive conditions such as mitral stenosis, decreased plasma protein concentration from any of a number of causes, increased pulmonary blood flow against a fixed resistance such as, again, mitral stenosis, and constriction of the pulmonary veins or venules. The other mechanism is a decrease in capillary impermeability to protein. This occurs in response to certain poisons, such as war gases. Changes in capillary permeability resulting from nervous reflexes have been postulated,[6] but have little experimental documentation. Increased capillary permeability due to anoxia, as reported by Landis[7] and Warren and associates,[8] has not been confirmed by recent investigators.[9, 10, 11]

A number of events occur during experimental fresh-water drowning, each of which has been shown to cause an excess of capillary hydrostatic pressure above colloid osmotic pressure under other conditions. These factors are anoxia, hypertension, bradycardia, increased blood volume, decreased plasma protein concentration, and respiratory obstruction. In regard to anoxia, Lougheed and co-workers[12] and Swann and associates[13] have shown in experimental drowning, using dogs, that the arterial oxygen content declines progressively to values which have been shown in the heart-lung preparation to cause left-heart failure.[14] These authors have also demonstrated that hypertension occurs, with the systemic arterial pressure rising as high as 300 mm. Hg during the animal's initial struggles. Hypertension may cause additional strain on the left ventricle. In fact, the injection of Adrenalin is a standard technique for producing experimental pulmonary edema due to hypertension. The animals of Lougheed and Swann exhibited immediate, marked slowing of their hearts. Bradycardia has been shown to cause elevated pulmonary venous pressure.[15] In regard to increased blood volume, the experimental studies of Swann and associates[13] and Karpovich[16] have shown that the blood volume increases and may even be doubled by water entering through the lungs during the short time it takes for an animal to drown in fresh water. (This holds true only for drowning in fresh water. Swann and collaborators have shown that the blood elements become more concentrated in sea-water drowning.) The plasma protein concentration decreased as the blood became diluted. Both of these factors, increased blood volume and decreased plasma protein concentration, tend to create an excess of capillary hydrostatic pressure over colloid osmotic pressure.[11] Respiratory obstruction has been shown experimentally to induce elevation of pulmonary venous pressure and pulmonary edema in dogs.[11]

The evidence for changes in capillary permeability is small. Cot[1] has called attention to the high protein content of the fluid found in the lungs of drowned human beings. This is a finding, however, in most far-advanced types of pulmonary edema, regardless of etiology.[17]

Swann and associates have shown that the effective inferior vena caval pressure rises in experimental drowning in dogs, indicating the existence of right-heart failure. The crucial experiment, measurement of the pulmonary venous pressure during drowning to determine the condition of the left ventricle, is yet to be done. One would expect the pulmonary venous pressure to be elevated above the colloid osmotic pressure, an indication of relative failure of the left heart.

From the above reasoning, it would appear that digitalis, venesection, diuretics, and oxygen would be of value in the treatment of pulmonary edema following near-drowning in fresh water. The use of oxygen or oxygen-helium mixtures under positive pressure[18, 19] can be considered in cases in which the blood pressure is not below normal. The rationale of such therapy is based upon the fact that an elevation of intrathoracic pressure decreases venous inflow to the heart,[20] thereby decreasing pulmonary blood volume and pulmonary capillary pressure. In cases where much froth is present in

the respiratory tree, the use of antifoaming agents such as vaporized ethyl alcohol may be of value.[21, 22]

CONCLUSIONS

A case of pulmonary edema associated with near-drowning in fresh water has been presented. The literature has been reviewed, and possible mechanisms of etiology have been discussed. Suggestions for therapy have been mentioned.

We wish to thank Dr. Forrest H. Adams and Dr. Francis J. Haddy for their encouragement and helpful suggestions in the preparation of this case report.

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A ROCKING BED RESPIRATOR FOR USE WITH PREMATURE INFANTS IN INCUBATORS

Description of Apparatus

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THIS paper describes an apparatus for applying the Eve tilt-table method of resuscitation to small premature infants. The method as originally suggested by Eve[1, 2] has been widely applied to adults. Recently it has been gaining acceptance for use in delivery room resuscitation of the newborn infant. Apparatus has been described for such use.[3, 4, 5]

The method is also useful in resuscitating small premature infants who present persistent apnea. No mechanical apparatus has been available for accomplishing this *inside an incubator*.

When accomplished simply by holding the infant in the hand and rocking back and forth the method is fatiguing if it must be prolonged. Simple manually operated tilt-tables serve well enough for brief emergency use but mechanically driven apparatus has great advantages where a prolonged application is necessary.

The rocking bed shown in Figs. 1 and 2 was designed and constructed for use inside the Isolette incubator. Figs. 3 and 4 show a 3 pound premature infant on the rocker in an Isolette.

Peculiar to the requirements was the need for a machine *small enough to be used in the incubator* and operable in an atmosphere of increased oxygen tension. The latter requirement precluded using an electric motor for the drive. A plunger or push rod from the outside would have necessitated modification of the incubator. The present machine avoids the above difficulties by using suction as the source of power.* It operates by means of a diaphragm type windshield wiper motor. As little as 8 pounds negative pressure is sufficient for its operation and therefore the usual hospital suction apparatus is adequate. Most such machines produce enough suction so that with a Y-tube arrangement both suction and power for the resuscitator may be obtained at the same time.

The motor is mounted immediately under the tilt-top for the sake of compactness. The oscillatory movement of the windshield wiper motor arm is transferred to the tilt-top by way of a heavy braided nylon cord running under two pulleys. The motor supplies power for the oscillation in one direction and a pair of obliquely mounted springs return the table top to its opposite extreme position against braking action of the return stroke of the motor.

A speed control is mounted on the upright and permits of operation from 10 to 50 cycles per minute.

The attachment of the nylon cord is adjustable in a linear direction to per-

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*Oxygen concentration in the incubator operating at 40 per cent is lowered approximately 5 per cent by the operation of the suction driven motor. If necessary, this can be compensated by increasing oxygen by ½ to 1 liter per minute.

mit alteration of the angle attained by the tilt-top in its oscillation.

The tilt-top itself has two adjustable shoulder supports moveable in two planes and an adjustable cross bar which help in supporting the infant. bandage is placed across the hips and over the hooks on the side of the tilt-top. The three supports plus this cotton band serve to keep the infant in place. The entire unit is designed to fit inside the Isolette incubator and

Fig. 1.

Fig. 2.

Over these supports is placed a piece of ordinary bed padding. The infant is placed on the padding, the supports adjusted, and a piece of elastic cotton the only external attachment is the rubber suction hose which is brought in through one of the vent holes in the side of the incubator.

DISCUSSION

It should be emphasized that the rocking bed method is useful for only a selected group of premature infants. It is useless in the absence of an open airway. It cannot improve the situation when an infant is vigorously making its own efforts to breathe. It is for the apneic infant, the one who is not adequately attempting to breathe, that the machine is useful. This situation occurs with narcotized infants at

Fig. 3.

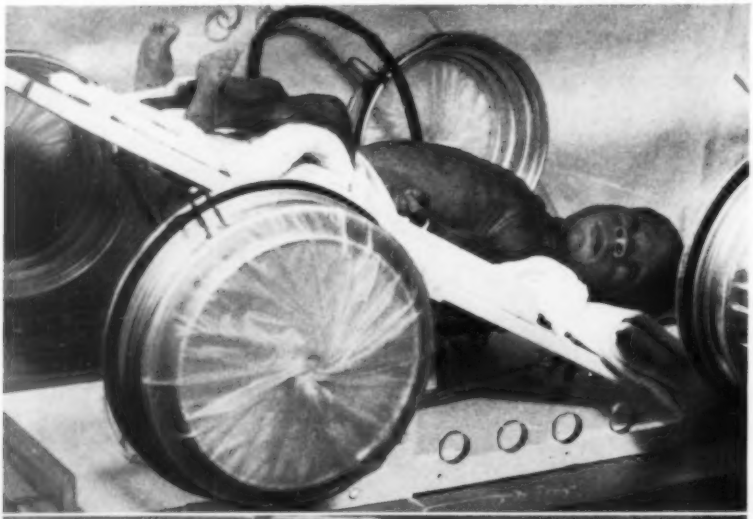
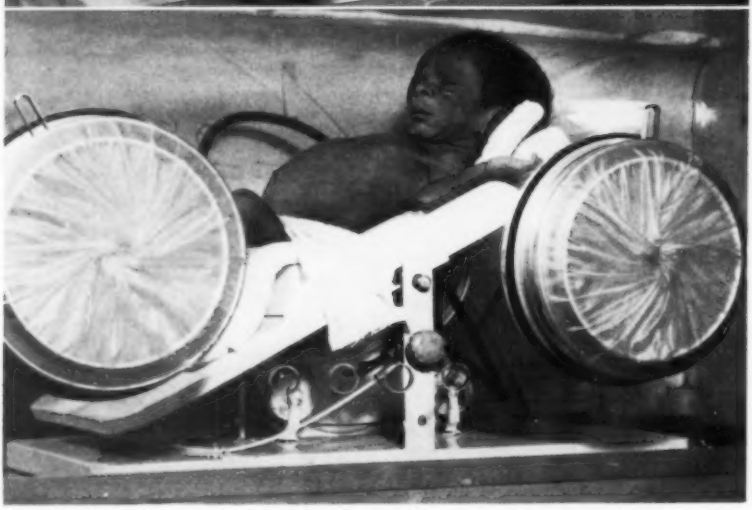


Fig. 4.



and after birth and not infrequently with very small premature infants after the first three or four days when fatigue becomes a factor. Such infants, whose prolonged apneic spells produce marked and more or less constant cyanosis, are often greatly improved on the tilt-table and may be maintained for prolonged periods.

During the past year we have used the machine on a number of apneic infants. In some cases the response has been immediate and excellent. Some infants have been maintained for many hours and have finally improved sufficiently to be able to continue without further aid. In other instances the machine has improved the infants' color but they have not recovered to the point of being able to maintain themselves and have finally died. The degree to which the machine produces actual pulmonary ventilation in the small premature infant is an open question.* It may function partly by supplying external physical stimulation to the activation of the infant's own respiratory mechanism or by mechanically improving cerebral circulation.

In its applications to adults the rocking bed has been rather thoroughly investigated. Eve and Killick[2] showed that rocking produced at least as good a respiratory exchange as other methods of artificial respiration. Comroe and Dripps[6] reported that tidal flow of air produced is greater than that produced by the Schaefer method. No data are available for infants.

The thoracic wall of the premature infant has relatively little elasticity. Physical compression of the chest as a means of resuscitation or artificial respiration is not satisfactory. The rocking bed seems to offer a reasonable solution for these small infants. Observation suggests that pulmonary ventilation is actually attained but objective data are lacking.* In the absence of objective evidence of ventilation other than improvement in color and heart action, any appraisal of any apparatus or method must indeed be guarded. Enthusiasm for what seems to be a useful method must not be permitted to relax attention to observation, aspiration, and every other factor of good premature care simply because there is an additional means of possible resuscitation at hand.

*Studies are in progress.

SUMMARY

An apparatus has been constructed for applying the rocking bed method of resuscitation or artificial respiration to premature infants within the Isolette incubator.

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*Studies are in progress.

CARDIO-ESOPHAGEAL RELAXATION. TREATMENT WITH AN INEXPENSIVE CHAIR

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SINCE Neuhauser and Berenberg[1] began to emphasize the importance of cardio-esophageal relaxation (chalasia) as a cause of vomiting in infants, additional workers[2, 3, 4, 5, 6] have added to the growing list of such cases. The recognized incidence is such that a report hardly is justified on the basis of its rarity.

The clinical courses of these patients are quite similar.[5] There is still uncertainty as to the etiology,[5, 6] and the causes may be multiple.[5] Although Allen[3] reported one case with improvement after atropine therapy, response to drugs usually is unsatisfactory.[2, 5] Keeping the infant in an erect or semierect position during and after feedings routinely gives excellent results.[5, 6] Thickened feedings are beneficial.[5] As a rule, such therapy can be discontinued in about one month. Therefore, the management of this disorder is primarily one of positioning the infant during this relatively short period of difficulty. Various methods have been used to achieve this end. Neuhauser and Berenberg[1] suggest the use of a pillow and harness. Hill[4] describes a support made from plaster and metal. Davies[6] presents a canvas chair.

When a case of chalasia presented itself at this institution the maintenance department cooperated in constructing a simple, inexpensive chair which we found quite easy to use and of marked benefit to the infant. It answers the need for infant comfort, ease of cleaning, ease of construction, and low cost. This chair is shown (Figs. 1 and 2) along with diagrams (Figs. 3 and 4) of its construction. Ordinary needs do not justify a hospital's keeping such equipment in constant supply, but this can be constructed cheaply and within a couple of hours. The following case is one in which such a chair was used.

CASE REPORT

N. L. B., a white female, was delivered at the U. S. Naval Hospital, Memphis, Tenn., on July 13, 1953. The mother was a 22-year-old gravida ii, para i, and the pregnancy and delivery were uneventful. The birth weight was 3,650 grams. The hospital course was uneventful for the first 10 hours, at which time the infant vomited a small amount of mucus. This was not excessive, so glucose water feedings were begun at 12 hours, and given at four-hour intervals. The first two feedings totaled 90 c.c., and were retained. After these she regurgitated all water intake. There was no abdominal distention, meconium stools were passed, and the infant appeared in no distress other than being hungry. On July 15 Farber's test was positive for cornified epithelial cells. Erect and flat roentgen views of the abdomen and a barium enema revealed no abnormalities. An upper gastrointesti-

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nal series was done with Lipiodol instilled via a gastric tube. It was negative except for the reflux of some of the Lipiodol into the esophagus. This brought up the possibility of chalasia, but I was not impressed with this possible explanation for the vomiting. Water feedings were given by slow drip, using a polyethylene gastric tube. With this routine there was improvement for eighteen hours, but vomiting recurred. On July 16 bilateral subdural taps were negative. Throughout all this time hydration was maintained with glucose and saline solutions given by hyperdermoclysis and intravenous plasma. Serum sodium, potassium, and chlorides were normal on July 17. The following day the upper gastrointestinal series was repeated. This time a dilute barium mixture was given by nipple feeding, and the cardio-esophageal area was studied with the patient erect, supine, and in a Trendelenburg position. Reflux into the esophagus was observed in all situations. This seemed conclusive evidence for a diagnosis of chalasia. Accordingly, the patient was kept in a semierect position, using pillows and towels as supports, and started again on glucose water feedings. They were retained for twenty-four hours, and routine house formula (evaporated milk, 9 parts; boiled water, 15 parts; with 5 per cent carbohydrate) was begun. This, too, was retained. The only difficulty was in maintaining the infant's position. Therefore, on July 20 a special chair (Figs. 1 and 2) was

Fig. 1.

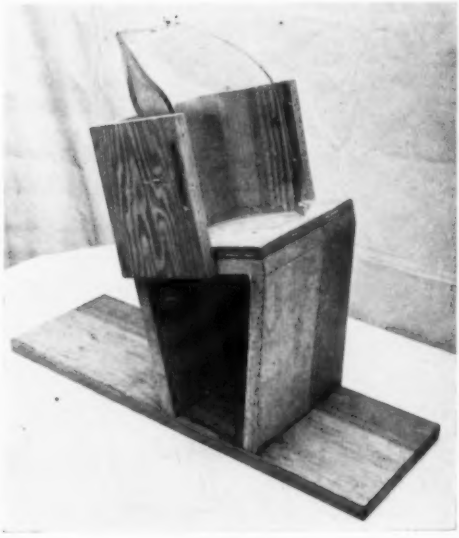

Fig. 2.

Fig. 1.—N. L. B. is shown at the age of 12 days. A diaper is used to line the chair. A foam-rubber seat cushion is in use at this time, but it is not necessary. A towel pinned through the apertures in the sides serves as the only restraining article. Note the freedom of movement allowed while maintaining adequate support. At this time the infant remained in the chair twenty-four hours a day.

Fig. 2.—Photograph of unoccupied chair. Plexiglass was used for the back support, as this material was available. It can be replaced by plywood or aluminum sheets such as those available for splints.

constructed. Using this supporting device the infant seemed much more comfortable, and her position was maintained with a minimum of effort. Her weight, which had dropped to a minimum of 3,410 grams on July 19, began to rise, and she was discharged on July 22. The chair was used for home care. At home, vomiting was infrequent and positional therapy was not required after the first month of life.

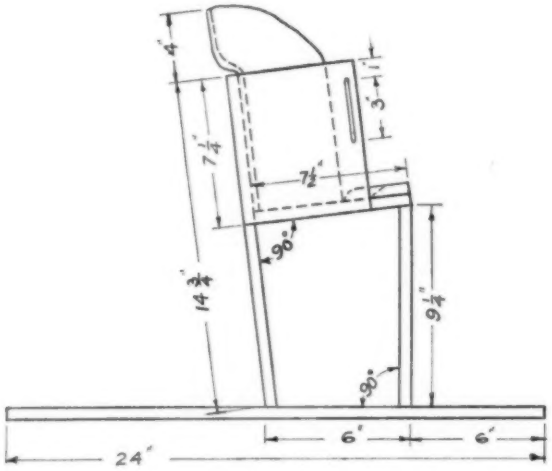

Fig. 3.

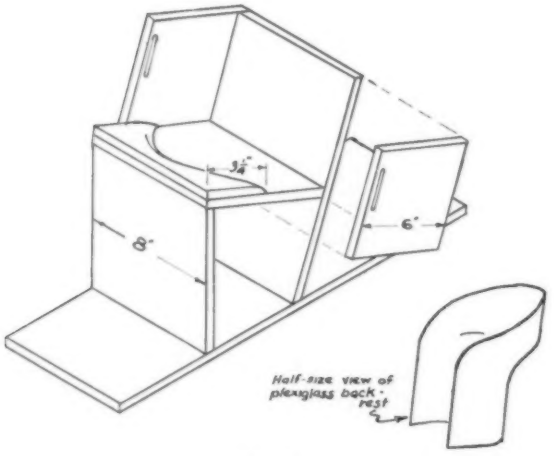

Fig. 4.

Figs. 3 and 4.—Diagrams of construction. The base was constructed so as to fit into a bassinet. Its dimensions can be varied as desired so long as stability is preserved.

Mr. H. E. Taylor, Head Carpenter, assisted in the construction of this chair.

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Medical Progress

EPIDEMIOLOGIC STUDIES IN DENTAL CARIES

VI. A Review of Intrinsic Factors as They May Affect Caries Progression

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FOR many years, certain careful workers in the field of dental research have been dissatisfied with the classical chemicoparasitic theory as the cause of tooth decay.[1, 2, 3, 4] A succession of reports has appeared to establish the concept that the tooth is not the inert structure which proponents of the chemicoparasitic theory have taught, and with recent years the evidence has become overwhelming. The findings show that the tooth changes its structure and composition after it has erupted into the oral cavity, and that these changes are conditioned by the body fluids. Moreover, these posteruptive changes may be correlated with the resistance or the susceptibility of the tooth to decay. These concepts which challenge the older theory have not been well received by most dental educators, nor have they become known to many persons not working in the particular field. In two recent authoritative reviews emanating from official dental circles, reference to the responsiveness of the tooth to caries through physiologic means has been ignored or dismissed as irrelevant.[5, 6]

It is important that both physicians and dentists, as well as all other workers in the fields of health advancement, know of the recent findings relating to the reactivity of the tooth structure to its internal environment. There is reason to hope that through a new approach based on the physiology of the tooth, more can be accomplished to check tooth decay than has been done during the past two generations while attention and therapy have been focused entirely on the regional consideration of the tooth.

This review has been written to present and consider the evidence that the erupted tooth does respond to changes in its internal environment, and the manner in which such changes may affect its caries resistance.

I formerly was identified with clinical studies of tooth decay among different groups of hospitalized children at the State University of Iowa.[4, 7-17] In these studies, dental records were more elaborate and more complete than is customary. These records made it possible to follow the serial course of caries for periods of years, not only for a given child's mouth, but for specific cavities as well. Thus the pattern and timing of the evolution of a single cavity could be observed. When the findings were contrasted with those from comparable

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studies made by ourselves dealing with school population groups, it was noted that tooth decay progressed more slowly in the mouths of the children living under hospital regimentation than it did among the school children.[7, 11] Developmental pits and fissures tended not to become carious with the passage of time, nor did preexistent caries tend to progress among the regimented subjects. Similar observations were made from the mouths of children regimented through life in custodial institutions.[12] When regimentation was most complete, e.g., among diabetic children whose food intake was quantitatively and qualitatively supervised, actively carious lesions ceased to progress within a few weeks after regimentation was established, and remained arrested in open, untreated cavities for months and for years thereafter.[7, 9] The exposed dentin at the bases of such cavities became stony hard coincident with the arrest of caries, and remained so as long as the caries remained inactive.[17] Our earlier observations had demonstrated the safety of leaving test cavities unfilled, so long as the general dental response of the individual's teeth was good.[17] These observations would not have been possible had we not preserved records which permitted accurate serial comparison of cavities for long periods of time, or if all cavities had been filled promptly in accordance with good dental practice.

Within the past ten years, a study of the progression of caries among 250 teen-aged children was made among the population of a custodial institution for the feeble-minded.[13] During the median twelve months of a five-year study period, sixty-five girls received first no refined sugar whatever for six months; then for a similar period each subject ingested almost 4 ounces of refined sugar daily with meals. Meticulous dental studies failed to indicate any significantly different rate or pattern of caries advance among these girls with marked changes in sugar intake than was evident among the control subjects whose diets were not modified, or among these experimental subjects during the fore- and post-periods of observation when they received the usual institutional diet. Moreover, among the whole group of subjects studied, more than two thousand Lactobacillus counts from saliva samples failed to show correlation between the magnitude of the counts and the net rates of caries advance.[14]

Our studies had led us early to postulate that tooth decay is conditioned as much and probably more by conditions operative from within the body of the individual than by intraoral conditions.[4] None of our studies has offered us evidence that oral cleanliness, prevalence of Lactobacilli, or levels of sugar ingestion had any significant role in determining rates of caries advance among children whose net dietary intake approached ideal levels for normal nutrition. Let it be recognized that such nutritional levels exceed the excellence of the diet of the average child in various particulars: it is assumed that it is the exceptional child who will not profit through betterment of his customary diet practices.[23, 24*]

The reader will recognize the discrepancy between the views just ex-

*The studies of institutionalized children were made possible by a grant from the Sugar Research Foundation.

pressed and those held and taught by most dental authorities. The conflict of opinion is not easy to reconcile. Our studies have been undertaken with no precommitment of opinion favoring a regionalistic concept of caries causation, and without attempt to reconcile our findings with earlier teachings. Our methods of study have provided information not previously assembled regarding the evolution of the individual caries lesion. In contrast, the validation of concepts supporting the chemicoparasitic theory has been derived chiefly from cross-sectional studies of caries counts within population groups, with notation limited to the first recognition of enamel defect, with no consideration given to the subsequent course of the lesion, and without identification of the lesion with an individual mouth. The errors inherent in the interpretation of dental statistics have been discussed elsewhere.[14, 15, 18]

Basically the question to be considered in this presentation centers itself around whether or not the tooth changes its chemical or structural composition significantly in response to alterations in its liquid environment, and, if so, whether such changes may affect its susceptibility to caries.

The earlier workers had assumed that because there is no vascular channel between the enamel and the pulp of the tooth, there is no means for producing posteruptive changes in the enamel through metabolic activities. Distinction was not made between those metabolic changes which call for cellular activity, and those which proceed through the processes of diffusion and ion exchange. Kronfeld,[18] writing in 1939, portrayed the point of view which had characterized the preceding half century of dental thought, and which still is prevalent:

"The enamel of the adult tooth is devoid of circulatory channels; in a biologic sense it is no longer in connection with the rest of the body but merely forms an inert, protective covering over the more vulnerable, inner part of the tooth. It cannot be altered from within, by way of the vascular system of the pulp with which it is no longer connected. For the same reason additional calcification of the adult enamel is impossible. The structure and the composition of adult enamel of the erupted tooth cannot be altered by nutritional means."

Seven years later, another dental educator,[19] a biochemist, made the following statement:

"The idea held by most of the earlier histologists that enamel is a completely inert substance, entirely lacking in organic matter, was a challenge to many workers who believed that this view could not be correct. . . . Experiments . . . indicate a progressive change in enamel after eruption. . . . Thus permeability studies indicate clearly that with increasing age, dentin becomes denser and less permeable, and that enamel probably undergoes a similar change."

To reconcile these two expressions of opinion, one would need to interpolate the idea that newly erupted enamel is not "adult," and that posteruptive changes do occur in enamel during its progress toward maturation. Evidence will be presented here to show that the enamel changes its mineral content recurrently throughout the lifetime of the individual. Less easy to demonstrate but no less probable is the concept that the enamel of the adult tooth has a greater mineral content and corre-

spondingly becomes less permeable than is the enamel of the young tooth.

The enamel of the sound tooth crown is readily permeable to water, and there is no reason to doubt that there is a steady passage of water (from the extracellular fluids or from the saliva) through the enamel in each direction. Such water carries with it the ions and molecules it holds in solution. That such molecules may have considerable size is shown by Wainwright and Lémoine's[20] demonstration that urea tagged with C^{14} passed through intact enamel from the oral cavity inward within ten minutes after a solution of that substance had been brought into contact with the enamel surface. Similarly, Berggren found that the phosphate ion (P^{32}) penetrated the enamel quickly, either from within or without; apparently most of it entered through the pulp and travelled centrifugally (and without specific vascular channels for its transport!). Even the molecule of tetanus toxin was shown to traverse the enamel, if initially it was mixed with a high concentration of glucose.[21] A spectacular demonstration of enamel permeability from its outer surface inward was furnished by Bartlestone's experiment, using in vivo the intact upper cuspids of cats, the tips of which were immersed in tiny plastic cups containing radioiodine. With no avenue for iodine uptake possible other than through the intact enamel, he demonstrated that the I^{131} got into the circulation and was transported to the thyroid gland where it concentrated in sufficient amount to activate the Geiger counter within one and one-half to two hours after the experiment was started. Sectioning of the teeth and jaws subsequently permitted demonstration through radioautography that the channels of ingress had been through the sound enamel.[22]

Dissolved substances also can reach the enamel from within the tooth by way of the dentinal fluids. Many studies using internally administered radiophosphorus have demonstrated that fact. The anatomy of the tooth is adapted toward such interchange of fluids by way of the dentin. The dentinal tubules initially are highly permeable to fluid from the pulp, and at the dentino-enamel junction these tubules anastomose freely to form a plexus with considerable internal fluid space. The dentin has some measure of elasticity, and with chewing the compression transmitted through the enamel serves to disseminate the dentinal fluids throughout all patent channels.

Thus it is shown that the enamel has means for interchange between its substance and the fluids of the pulp; moreover, that its apparently impervious surface will permit ingress and egress of fluids. There also is ample evidence that both the enamel and the dentin take up ions from the fluids which perfuse the tooth, and in exchange may give up like ions from the mineral salts previously deposited in them. It is reasonable to assume that in the case of the enamel most such mineral exchange occurs in the regions surrounding the enamel rods. It will be recalled that the enamel is made up of the highly dense rods or prisms which extend radially from the dentino-enamel junction to form a resistant, hard covering for the dentin and

pulp. Between these rods is a reticulum of keratin-like material which becomes impregnated with mineral salts after the enamel rods have become mineralized. There is indirect evidence that this reticulum and other organic tissue in the enamel zone become progressively more mineralized as the posteruptive life of the tooth is extended. Likewise, if the extracted tooth is exposed to weak acid, it is the mineral of the interrod substance which first is attacked.

The dynamics and the time factors related to the mineral exchanges in the enamel remain subjects for careful study. There seems to be room for some analogy between the posteruptive mineralization of teeth and the progressive mineralization of bone. Just as the age at which bone achieves its adult level of mineralization is dependent on the degree of intake and of uptake of mineral and of associated factors,[25] so, too, we may predicate that the secondary mineralization of enamel may vary as to its completeness in terms of age due to conditions reflected in the general body metabolism.

There is less controversy regarding posteruptive changes in the composition of dentin although most authorities pass over such changes as irrelevant to the initiation and advance of caries. Dental histologists describe two progressive changes which occur in the dentin after the tooth has erupted.[26] These are referred to, respectively, as the deposition of secondary dentin and the sclerosis of dentin already formed. *Secondary dentin* is that which is formed posteruptively through the mesial elongation of the dentinal tubules. It tends to be uniform in pattern, corresponding with that of the primary dentin of the young tooth. Under areas of peripheral irritation, however, the secondary dentin is irregular in structure and localized in deposition. *Dentinal sclerosis* is the process of occlusion of the dentinal tubules through increased mineralization. The newly erupted tooth presents no sclerotic dentin; the sound adult tooth, on the other hand, shows essentially complete sclerosis of the coronal dentin.

Both secondary dentin and sclerosis develop in response to intra-oral stimuli which can cause shock to the pulp. Many such stimuli are physiologic and inevitable, such as physical trauma from chewing or the lateral contact of one tooth with another, change of temperature from hot or cold liquids or foods, physicochemical stimuli from the action of hypertonic solutions, et cetera. Such agencies would inflict pain to the pulp unless adequately insulated from it through dental tissue. The dentinal tubules immediately underlying zones predisposed to trauma soon develop sclerotic changes which spread gradually until the whole tubule is affected. Typically, tracts of tubules rather than individual ones are affected concurrently. As a response to the same stimulus there is a tendency for secondary dentin to form at the base of the affected tubules, both changes serving to insulate further the pulp from the site of peripheral irritation. Clinical and laboratory evidence indicates that dentinal sclerosis also protects the region against the inroads of decay. Drain[17] found hardening of the exposed dentin in open cavities which had become caries-resistant, and used that finding as an index of arrest of decay.

Sognnaes[27] observed the same change in rat teeth which had become carious due to the use of coarse particle diets, when the diet regimen was changed to fox chow of fine particle size.

Histologically one notes distinctions between the appearance of the dentin adjacent to active caries and that which has become arrested. There may be some sclerosis lateral to an active cavity, but the tubules at the base of the cavity do not present an adequate barrier to the inward spread of the caries lesion. In areas of arrested caries, on the other hand, the dentinal tubules at the base of the cavity are so occluded that they fail to take up stain.[28] Hardness studies also indicate increased physical density of such sclerosed areas.[29] With caries limited to the enamel, the underlying sclerosis often is sufficiently dense to have prevented any degree of dentinal involvement.

If a filling is placed in the tooth of an experimental animal, and several weeks later the tooth is removed and sectioned, it will be found that the dentinal tubules underlying the filling have become fully sclerosed. Similar changes in the human tooth after the placement of fillings explain the gradual loss of unpleasant response to hot or cold liquids in contact with the surface of the recently filled tooth. Bodecker and Applebaum[3] have applied the term "protective metamorphosis" to those changes which result in occlusion of the dentinal tubules. Sclerosis is a progressive change which is initiated when the tooth first erupts into the oral cavity, and which tends to continue until the whole substance of the dentin has lost its capacity for the ready transfer of liquids between the pulp chamber and the periphery of the tooth.

The rate and effectiveness of the development of dentinal sclerosis vary from one individual to another, and in the same person from one period of life to another. Our findings lead us to believe that the excellence of mineral metabolism is a deciding factor in the effectiveness of the process. In the individual whose metabolic processes are proceeding at an optimum level, one would expect the tooth not only to reach an adult state of mineralization earlier in life, as is true with bone composition,[25] but also would expect the dentin to respond at points of predisposition to caries (e.g., pits and fissures) with regional sclerosis. Such a tooth then would escape caries in an environment where the less well-sclerosed tooth would become carious. Where conditions in a tooth are such that caries has gained a foothold, one would reason that if the caries defenses had been adequate the caries would never have gotten started. By the same reasoning, once caries is active, the only manner in which it would become arrested spontaneously would be through a betterment of facilities for sclerosis of the underlying dentin. In view of the fact that each of us tends to develop and maintain a type of life and habits of eating which are convenient for us to maintain, there is little likelihood that abrupt changes in such patterns of living will be instituted unless brought about through imposed measures, or through change of place or manner of residence. Considering all of these points, it is evident that tooth decay will tend to follow patterns which more or less characterize

the individual person, and that arrest of caries will not be observed frequently except among those whose conditions of life have been changed and brought under some form of regimentation. Periodic changes in one's susceptibility to caries can be attributable to seasonal changes in diet habits or food availability, amount of exposure to sunshine, lessening or augmenting of upper respiratory infections, or to any other factors which can affect the over-all efficiency of the total body economy. Although excellence of diet is a highly important agent in the maintenance of such economy, by no means is it the only one which should be considered.

Sclerosis of dentin leads to increased density of the corresponding region. This density manifests itself in the resistance to penetration by the exploring tine,[17] changes in permeability to light and to x-ray,[29] and to the uptake of radioisotopes.[30] No student of tooth morphology disputes the occurrence of posteruptive changes in the dentin, even though there is lack of agreement as to the significance and function of the process. Rather than interpreting it as a pathologic change, as was voiced by earlier investigators, there seems little doubt that it represents a physiologic "ripening," or a process of posteruptive maturation of the tooth, resulting in: (a) immediate regional resistance to caries-instigating agencies, and (b) lessened susceptibility of the mature tooth to caries attack. Whether or not an analogous process occurs in the enamel has not been shown beyond dispute, although there is evidence to support such a view.[31] Yet even though the enamel had no power to develop protection for itself, the defense powers of the dentin could be sufficient to avoid the advance of caries and to protect the pulp from bacterial invasion and destruction.

Radioisotope tracer studies have provided a most valuable tool for the study of physiologic changes in the tooth. Many of the findings mentioned in the preceding paragraphs were deduced from the measurement of uptake of radiophosphorus (P^{32}). To avoid confusion of ideas, specific citation of some of the relevant findings has been delayed up to this point.

Radiophosphorus, when given as the tagged phosphate ion either orally or parenterally, is disseminated rapidly throughout the body. It mingles with the mobile phosphate ions of the body in a quantitative ratio, proportioned according to the amount of the isotope absorbed versus the total amount of nonradioactive phosphate present in the body fluids. From the body fluids it transfers to the phosphate-containing tissues, being exchanged therein for phosphate ions already fixed in such tissues, and again in the ratio that the radioactive ion bears to the nonradioactive form. The rate of incorporation into each tissue is determined by the rate of fluid exchange in such tissue, and also by the availability of fixed phosphate for exchange. Various studies have recorded the rate of such transfer, the degree of lability or of stability of the radiophosphate in the various tissues of the body, and the time required for various phases of exchange. In growing tissues, the radiophosphorus not only exchanges with phosphate already incorporated in the tissues, but it also becomes a part of the phosphate forming the newly formed increments of the specific region.

Bartlestone[32] recently has reviewed the findings of dental investigations using radioisotope techniques. The following comments have been summarized from this review, and sup-

plemented by some more recent articles. Consideration has been limited to studies dealing with radioactive phosphorus and calcium, because findings from such studies are sufficient to illustrate the discussion in the earlier part of this presentation.

Radiophosphorus is taken up by the teeth, as it is by other parts of the body. The amount of uptake is proportional to the bulk of the tooth in comparison with the dose administered. Thus the amount will vary from one species of animal to another: for the cat, about 0.02 to 0.05 per cent of the administered dose was found in the teeth, with about eight times more in the dentin than in the enamel.[33] More is taken up in growing parts of the teeth (such as the rat incisor) than in tooth substance already formed.[34] None appears to be taken up by the organic portion of the tooth.[41] Of that which is taken up, part is labile, paralleling that present coincidentally in the blood; part is stable, remaining demonstrable as a part of the tooth for weeks until it is exchanged for nonradioactive phosphate subsequent to its deposition, or until it becomes nonidentifiable through exhaustion of its radioactivity.[44] The rate of disappearance of the radioisotope from the tooth permits estimation of the "turnover rate" of the ion for a specific tissue, regardless of whether such turnover relates to the ordinary form or to the radioactive form of the ion. There is evidence for a slow but yet an appreciable turnover of phosphate in rat molars, slower in the enamel than in the dentin.[34, 41] Radiophosphorus has been shown to enter the tooth from the pulp, the pericementum, and the enamel.[35] Dentin exposed because of caries has taken up more than has the intact dentin[35]; pulpless teeth have taken up less in vivo than have teeth with normal pulp.[34, 35] In the dentin, under similar conditions of administration, most P^{32} has been found taken up by the circumpulpal zone, the least in the area of attritional cone; parallel amounts and patterns of uptake were found with teeth in vivo or in vitro.[37] The degree of uptake has been found inversely proportional to the regional density of the dentin, and also to the size of the crystals which comprise the mineralized portion of the structure.[38] It is presumed that the phosphate ions become attached to the exposed crystal surfaces, first by a process of adsorption, later through incorporation by replacement of ions already a part of the crystal structure. Radiocalcium behaves qualitatively the same as does radiophosphorus. About one-fifth of the calcium and phosphorus of the hard tissues of the teeth is demonstrably exchangeable. The process is reversible, and apparently goes on continuously as a part of the perpetual interchange of ions which characterizes dynamic physicochemical equilibrium.[40] Exchange reactions in vitro evidently are independent of the pH of the solution. Armstrong[41] did not find the rate of exchange affected over a range of pH from 7.5 to 13.0. Besic[42] recently was unable to detect changes in enamel which was placed in contact with acid solutions, even at pH 3.58, if the solution of acid also contained a maximal concentration of calcium and phosphate ions; with less than the maximal concentration, on the other hand, lesions not dissimilar to caries were produced.

Bartlestone summarizes his review with the following statement:

"In light of the evidence presented, there is no longer doubt that enamel, dentin and cementum are in contact with the systemic circulation by way of the extracellular fluids and the saliva, and that the internal environment of the tooth can be influenced by systemic factors."

The potential effect of tissue electrolyte content on the occurrence of regional changes in the mouth is illustrated by the findings reported by

Besic,[42] referred to in the preceding section. Even in a distinctly acid medium, teeth failed to show signs of demineralization if the solution contained a sufficiently high concentration of calcium and of phosphate ions; with a lowering of the ionic concentration, demineralization progressed. This finding is a corollary of that reported by Neuman, Boyd and Feldman[43] relating to the deposition of phosphate ions on chondroitin sulfate under conditions of varying concentrations of calcium ion present. Also the findings correlate with a clinical observation concerning the formation of salivary calculus. Drain was struck by the rapidity with which calculus formed on the teeth of the children with diabetes mellitus whose caries had become arrested; there was an inverse relationship between the activity of caries and the degree and rapidity of formation of calculus. We had assumed that this phenomenon was a reflection of the increased turnover of calcium salts in the body fluids of these child subjects.

The role of fluorides in the lessening of tooth decay has been publicized widely during recent years. Data seem to indicate that tooth decay is lessened through the incorporation of fluoride ion in the substance of the tooth during its pre-eruptive development. Other studies speak for a slowing of the caries progression rate indigenous to a population group through the topical application of fluoride solution to the tooth posteruptively. Representatives of the "regionalist" school of caries control attempted to explain the effect of the fluoride on the assumption that it served as an enzyme inhibitor, thus lessening the degree of fermentation within the mouth. Experimental studies did not substantiate the premise. It has been shown that fluoride ion can become an integral part of the crystalline structure of the tooth, and that such structure has greater resistance to physical destruction than has the unmodified form of the tooth mineral. Posteruptively, the fluoride ion can be taken up by the tooth surfaces with which it is brought into contact. Such uptake is through the same process of ion exchange which has been demonstrated through radioisotope studies. Hodge[44] points out, however, that the uptake is dependent on the application of a solution which is relatively concentrated, and that the process is reversible. In other words, once the environment of the tooth becomes such that the fluoride content of the oral cavity is less than that of the tooth, fluoride will be abstracted from the tooth rather than added to it. It should be emphasized that the use of fluoride is not a blanket panacea for the prevention of tooth decay; it may serve to decelerate the caries process, yet from one individual to another the degree of success in caries prevention is not constant.[45]

COMMENT

The interpretation of any body of data by the individual will be conditioned by one's background and philosophy. The viewpoints expressed in this review have been modified by my experience as a practicing pediatrician, and by my long-time association with children's dentists who had an open mind toward the question of caries causation and control. The approach to the dental problem has been similar to that for other childhood

disorders. The view has been held that although most simple complaints can be dealt with symptomatically, it is better to explore the potential causative mechanisms. Unless the cause is corrected, the complaint will tend to recur. Tooth decay has been considered as only one phase of the total health picture, and at all times the thought has been entertained that dental health is a reflection of health in general.

If tooth decay is an evidence of suboptimal health, as I believe, then the majority of our child population is experiencing something less than the best that health can offer. There are other evidences as well that such is the case. Physical growth certainly is related to general health levels.[46] As various groups of children come under more wholesome conditions of living, the physique improves, as is evidenced both through physical measurements and also through metabolic balance studies. Students of nutrition have shown that the diets of many children fall well short of the optimum for normal nutrition.[23, 24] Many children remain emotionally tense because of demands on their output which exceed their capacity, or because of discord within the home. Whether these factors bear a relation to the incidence of tooth decay may be disputed, yet each student of health will agree that the more ideal the conditions of living for the individual, the better the response one may expect. If the physician or dentist recognizes the importance of these environmental factors on the child's progress, he will make an attempt to recognize adverse conditions in the manner of life of each of his patients, and offer such assistance as he can toward correction.

Each child who comes to the physician, for whatever complaint, will profit from a careful survey of his habits of life and the degree in which they conform with the best standards of child hygiene. Likewise the examination of the child will include careful appraisal of his degree and rate of growth, as compared with standards from favored child populations.[46] Positive advice directed toward health improvement should be a part of each physician's contribution to his patient's welfare. If the physician is properly equipped to give such guidance, and if his patient and the members of the patient's household are able and willing to cooperate, much can be done toward health advancement. I believe that in such degree as hygienic practices are put into effect, there will be reduction of tooth decay as a corollary of other evidences of betterment of well-being.

Even though the physician were to offer advice and guidance of an effective nature to each of his patients, only the minority would observe his counsel. Every individual tends to persist in the pattern of life which convenience and necessity have imposed on him. Self-regimentation is seldom effective. Most can be accomplished through sound educational practices in the schools, and through gradual betterment of living conditions in a community. So long as substandard conditions persist among our child population as the rule rather than as the exception, there will be need for the treatment of tooth decay. The children's dentist is a most important ally to the physician in any program for the promotion of sound

health. If the teeth of the adult are to be sound, then caries must be treated during early childhood.[47] Damage to the teeth should be recognized and recorded by the physician, and the child referred to the dentist. Cavities should be cared for through conservative measures. The placement of a filling will lessen the likelihood that caries will progress in the affected zone. Wise measures should be employed to preserve the physical integrity of the teeth, both those of the deciduous and the permanent dentition. As a corollary, specific advice should be given relating to the provision of a complete diet, not through the prescription of mineral or vitamin pharmaceutical preparations, but through the wise and inclusive choice of foodstuffs. Diet advice should be directed toward the inclusion of essential foods, not toward the exclusion of food products which might be considered as caries-promoting.[48] I have found no evidence that the inclusion of refined sugar in the diet as an ingredient of prepared foods tends to promote caries initiation or spread. If the ingestion of sugar leads to the exclusion of other foodstuffs which are biologically more valuable, then its use should be curtailed. The physician or dentist who prohibits any foodstuff, however, incurs the risk of inducing unsuspected diet deficiency because of the limitation of calories thus imposed, and the utilization of biologically important foods as substitute sources of energy.

Both physician and dentist should cherish a spirit of skepticism toward extravagant claims for specific dentifrices or other regional agents for the prevention of tooth decay. The virtue of such agents lies primarily in their local cleansing properties. Research data have been misconstrued to suggest caries-preventing powers for dentifrices containing this or that ingredient. The American Dental Association, recognizing the harm from promiscuous and poorly founded advertising claims, recently has adopted a resolution calling the attention of the public to the inaccuracy of such claims. The editor of the *Journal of Dental Research* calls attention to the confusion between purported reduction in regional mouth acidity, on the one hand, and reduction in dental caries, on the other.[49]

The time has come for both the profession and the public to question many dental dogmas which have been presented as established fact. Although the newer findings cast strong doubt on the old, the picture is not yet complete. There still is need for much fundamental work on the nature of dental caries. New findings should lead each investigator to reappraise the total evidence, not in a spirit of defense for his convictions, but in one of a search for ultimate truth. We are gaining tools which should lead to an answer for the problems of caries. If each of us can approach these problems with an open mind and without being blinded by the errors of the past, more will be accomplished toward the conquest of dental caries than has been done through the use of the regional attack.

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Psychologic Aspects of Pediatrics

THE SOCIAL AND EMOTIONAL PROBLEMS OF THE EPILEPTIC CHILD AND HIS FAMILY

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IN EPILEPSY the eradication or control of seizures by medicines or by surgery is the capstone of treatment. However, the capstone of a pyramid does not float in thin air. It must have a broad base. For the epileptic such a base is the physical, emotional, and social well-being of the child and his family, a phase of treatment too often neglected by the doctor.

In epilepsy, more than with most diseases, the unit of treatment is the family. An epileptic child brings psychologic and social complications for those around him which are subtle, severe, and long lasting. Below and beyond the family is the widening substructure of friends, schoolteachers, acquaintances, and the general public. The conception of epilepsy which resides in the public mind is most important. For centuries the pyramid of therapy has had a foundation not of masonry but of rubble and sand.

As depicted in Fig. 1, in both cases the capstone of drug or surgical treatment is sound. The social-emotional treatment on the left is poor—secrecy, shame, and fear in the family. Underneath are public misconceptions and ostracism. In the case on the right, the family has a sense of security, courage, and hope, and there are public understanding and acceptance.

Let me hold up some of the pieces of rubble from under the capstone on the left. People say, "The cause of epilepsy is a complete mystery; there is no effective treatment; the disease and the disability are progressive; rest is best. The child should not attend school nor the adult have employment; a healthy child must not view a convulsion; mental deterioration is the rule; marriage and children are out." As illustrated in Fig. 1, such misconceptions are a crumbling support for medical treatment. Usually the doctor can say, "Evidence of brain damage is lacking; the child should maintain his good health and intelligence. With proper medication and with time the seizures should disappear and, given a right public attitude, he should be able to marry, to work, and, in short, to lead a normal life."

Wrong ideas, those that cause misery when spread abroad, can be as contagious and as harmful as pathogenic germs. Correction of false concepts requires public as well as individual efforts. Here is a problem of public health. More than with most diseases a better life for the

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epileptic depends on an improved understanding and attitude of the general public.

The sea of opinion in which the epileptic lives is beginning to feel the warming effects of the Gulf Stream of successful research and treatment of the past two decades. But the parents of the affected child may be last to accept the new warmth. Unhealthy sentiments such as fear, worry, shame, guilt, and despair give up their entrenched positions to hope and confidence only grudgingly. The episodic symptoms cause sharp fluctuations of emotion. A parent may unconsciously reject the child when his or her own esteem or social position is threatened. Unexpressed may be the thought, "This cannot happen to me. Let me put this terrible thing out of my thoughts, the child out of my presence." Guilt may follow realization that epilepsy came from his (or her) "side" or that the child's seizures followed some preventable accident.

A policy of hiding illness is the culminating injury inflicted by unhealthy sentiments. Secrecy has taken the place of the devils of old. Because patients and their relatives think they must remain in hiding, they do not take their rightful place in public campaigns against epilepsy. However, there is no security in secrecy. At any moment a seizure in public may tear off this cloak, exposing the illness in all its nakedness to a gaping public.

The social-emotional handicap for the epileptic is the more grotesque because so illogical and unnecessary. Epilepsy is a metabolic disorder and no more to be hidden than glycosuria or recurrent fever. In fact, a bout of high temperature without infection may be an epileptic seizure and as difficult to control as a convulsion. Dispassionately viewed, migraine is an autonomic epilepsy.

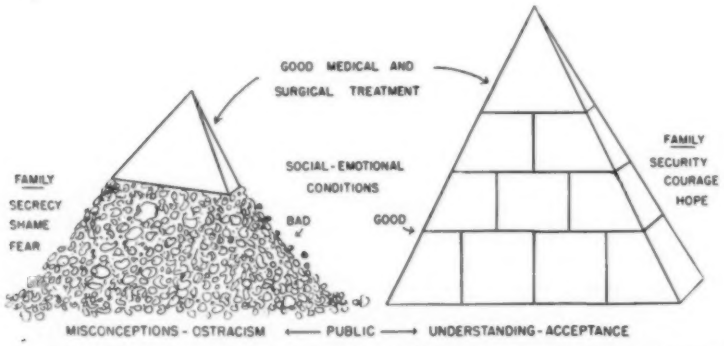

Fig. 1.—Schematic representation of pyramids of therapy. The capstone at the top of each represents good drug and surgical therapy. The supporting structure represents the social-emotional conditions, at the left destructive and at the right constructive. At the base of each is the influence of the general public.

EMOTIONS AND THE CHILD

What effect does the prevailing fear and prejudice have on the epileptic child? The answer varies with the age. Even the baby may learn to fear the attacks. Hippocrates stated this, "But little children—when they have been often seized

and feel its approach beforehand flee to their mothers—from terror and dread of the affliction, for being still infants they do not yet know what it is to be ashamed." The interruptions to play caused by frequently repeated petit mal may be frustrating and irritating.

Problems tend to increase with age. The young child may "get out of hand" because parents fear that "crossing" it will bring on an attack. Adolescence is a time of emotional rough waters; cross currents of overprotection in the home and rejection outside. What about traveling alone, dating, social events and late hours, smoking, drinking, swimming, automobile driving? A time-trusted guide is needed to prevent rupture of normal parent-child relationships. The age of 12 is not the time for the competent pediatrician to turn his epileptic child adrift in the turbulent current of adolescence.

What role do emotional factors play in the child's seizures? Emotional forces can and do precipitate seizures in those already primed. However, in the main, disturbing fears, anxieties, and frustrations are consequences rather than causes of attacks. If emotion is the whole cause, the condition is not epilepsy but hysteria. The pediatrician should be competent to handle all but the most flagrant of the emotional disturbances. Those mentioned are on the level of consciousness and not immersed somewhere in its depth.

Bad behavior may be a consequence of seizures, of brain injury, or of the strained relations engendered. Rarely, it may be a seizure itself. Differentiation is important. A child may be overactive, "always on the go," never satisfied, quarrelsome, destructive, disobedient, rebellious. Unhappy qualities such as these may be more difficult to explain and to control than the seizures. In such emergencies the help of an astute psychotherapist or social therapist for both mother and child is most welcome. To the extent that emotional problems arise out of the seizures, control of attacks by medication may bring a quick solution.

AID FOR THE PHYSICIAN

What special techniques or training does the pediatrician require? Of first importance are his own qualities that invite and inspire confidence. Parents and older children principally have three questions in their minds. Does our doctor know this subject? Can we believe what he tells us? Is his interest genuine? Close, unhurried attention to the details of the family life, the day-to-day problems of the parents, the distant bridges they want to cross now, the activities and ambitions of the child—these proclaim the doctor's real interest.

Of physical aids, by far the most important is the electroencephalogram. Tracings of the electrical currents of the brain allow the physician to speak with a certainty never dreamed of before. Approximately four-fifths of children subject to epileptic seizures display abnormalities during a twenty-minute recording. Minor deviations from the "normal" mean little. High-voltage waves, unduly slow or fast, so-called seizure discharges, tend to confirm a diagnosis of epilepsy made on clinical grounds. An alternate spike-and-wave formation recurring at the rate of three per second is diagnostic for petits, either actual or

potential. The slower two-per-second variation speaks for minor seizures, brain injury, and relatively poor prognosis. Spike discharges suggest cicatricial lesions; big slow waves, tumor or previous encephalitis; spike discharges over a temporal lobe during sleep support a diagnosis of psychomotor epilepsy. Abnormality confined to a certain area may encourage the neurosurgeon to operate and may tell him what portion of the brain to remove. The degree of brain-wave disorder bears some relation to the severity of the epilepsy and is a rough guide to therapy and to prognosis. Because the brain-wave pattern is an hereditary trait, records may help in tracing the heredity of epilepsy and in advising about marriage and children. Altogether, if (a large *if*) the technique of making records and their interpretation is in experienced hands, this procedure, properly subordinated to clinical experience, reinforces the work of the physician or surgeon and saves expensive hospitalization.

THE COMPLICATION OF BRAIN DAMAGE

Epilepsy per se is a metabolic disorder of the brain. Disability for this metabolic (idiopathic) group is due primarily to the seizures and secondarily to emotional and social complications. An organic (symptomatic) epilepsy is the result of changes in brain structures (such as trauma at birth or encephalitis) acquired after conception. Persons in this organic group face five possible complications: seizures, brain damage, mental defect plus emotional and social complications. The summation of these five may result in 100 per cent disability. In hopeless cases the doctor cannot preach hope. He is, in general, privileged to "cure seldom, relieve often, comfort always."

In addition to aiding in the social and emotional problems of individuals, the doctor must help to change public opinion and to cancel laws or rules that discriminate unfairly. The child, when adult, will meet problems of marriage and of employment. Doctors must now use their influence in smoothing the child's road of the future. Support of the leagues against epilepsy, one for doctors and another for the public, is important. The following cases illustrate problems involved:

After a series of convulsions, 7-year-old Fred was in a state of confusion for a week, able to walk and to eat when fed, but unable to answer questions or even to recognize his mother. His electroencephalogram was made up of discontinuous slow spike-wave discharges, ordinarily interpreted as representing a background of generalized neuropathology. The left-hand portion of Fig. 2 is a section from this record. The mother was advised by the pediatrician that Fred's condition was chronic and that institutional care would be desirable. This threw her into a panic. She already was allergic to this subject because a brother was in an institution as a chronic epileptic. We felt that an immediately bad prognosis was hardly justified, since conditions of stupor may succeed a series of convulsions, and even the slow spike-wave complexes may yield to therapy. The mother seemed to accept a more hopeful outlook. Fortunately, the boy's confused state cleared under Phenurone medication and his electroencephalogram also. The right-hand portion of Fig. 2, made five weeks later, shows a normal tracing. His intelligence score rose by 10 points to 106.

However, all this visible evidence of improvement failed to move the mother's foreboding. She interpreted shivering on the beach as a seizure; she thought his face at times had a foolish look; that his I.Q. should be higher. She was correct in complaining that his behavior at home was bad, with long periods of shrieking, reactions doubtless due to the tension of the mother's anxiety. When he was sent to a guidance home, his behavior was normal, but the deep-rooted anxiety of the mother continued in spite of efforts to explain and to reassure. She was referred to a psychiatrist who, not able to reach her through psychotherapy, administered a series of shock treatments. Now, a year later, the boy has been attack-free for eighteen months and the mother complains only of his poor grades at school.

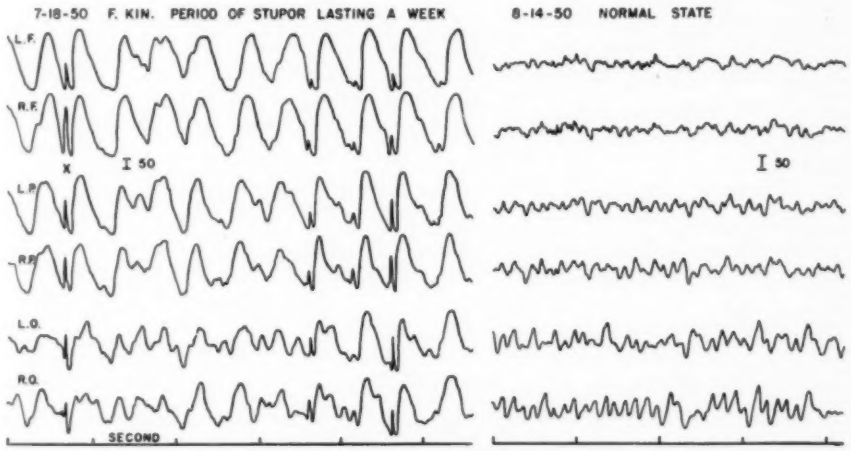

Fig. 2.—The electroencephalogram of Fred. In this and the remaining figures time in seconds is indicated at the bottom, the signal at the left represents the deflection caused by the indicated number of micro volts. Letters at the left indicate the placement of leads; *F*, frontal; *T*, temporal; *P*, parietal, and *O*, occipital. *L* is left and *R* is right. Explanations are in the text.

Jack, an 11-year-old, had a few convulsions in sleep but was without observed daytime seizures. The father, a physician, and the mother, sister of a chronic epileptic, were naturally deeply concerned. However the principal concern was for the boy's poor work in school where he was accused of laziness and inattention. His electroencephalogram was grossly abnormal (Fig. 3). Discharges of abnormally slow waves with scattered spike-wave complexes were represented clinically only by momentary wavering of attention and flickering of the eyelids. Placed on Milontin, dysrhythmia ceased, and his teachers were amazed by the improvement in his performance. His waking electroencephalogram was nearly clear of spike-wave discharges, but in sleep occasional, much faster, complexes appeared (right-hand panel of Fig. 3).

Pauline, a girl of 9 years, had a convulsion in early childhood that lasted two hours, but in the subsequent five years has had only five more. However, she seemed mentally retarded and was doing poorly in school. An I.Q. yielded a score of 54. An electroencephalogram made at this same visit was grossly abnormal. High-voltage slow spike-wave discharges were almost continuous in all leads, but their bad appearance was modified by the good feature of

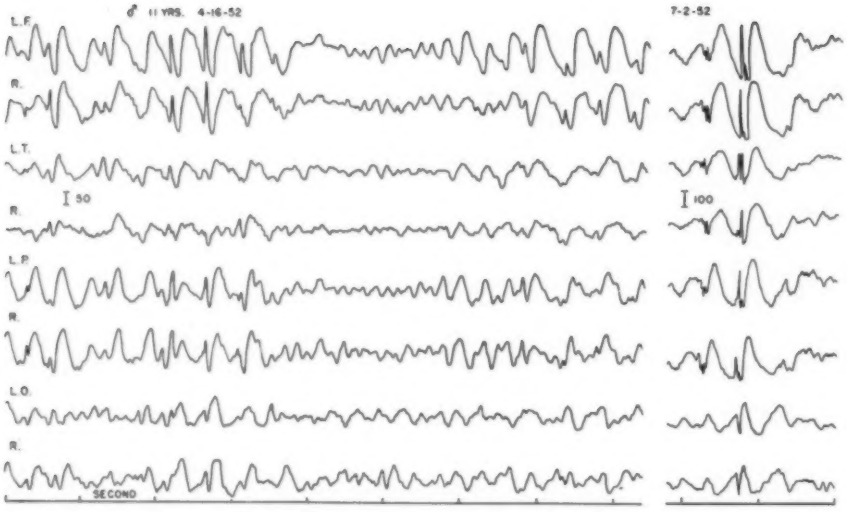

Fig. 3.—The electroencephalogram of Jack.

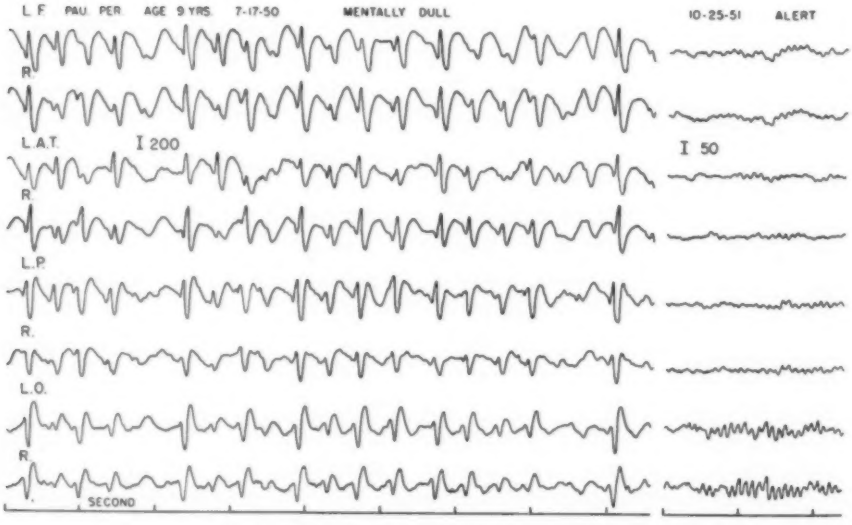

Fig. 4.—The electroencephalogram of Pauline.

generalized rhythmicity (left-hand portion of Fig. 4). Her convulsions called for phenobarbital or Dilantin, but her brain waves demanded Tridione. Placed on Tridione, her electroencephalogram became normal. The right-hand portion made fifteen months later was entirely normal. She was seizure-free but more important, Pauline, according to her mother, was near the top of her class in school.

EDUCATION

Outside the home the principal hurdle for the child and parents is education. "Must we tell the teacher?" "How would other pupils and their parents react to a convulsion?" "How many seizures will the school tolerate?" A psychologic evaluation and estimation of the intelligence is helpful. Is the sight of a convulsion a psychic trauma to other pupils? If so, what about the acts of violence and murder which children watch every evening on television? Properly handled, a seizure in the classroom can be useful as a demonstration of first-aid measures. To shield the child from all unpleasantness is a disservice to him. Association with the child who bravely carries on in spite of embarrassing episodes can be an educational experience in brave living.

Thus, if the child is receiving modern drug therapy with seizures reasonably controlled and if his intelligence and behavior are adequate, he (or she) should continue regular classroom studies. Three anxieties are outstanding.

EVENTUAL RELIEF

Time is on the side of the epileptic. Turbulent brain waves and seizures tend to improve with increasing age. Supported by competent medical treatment, the great majority of patients can be cured or substantially relieved of seizures.

MENTALITY

Eventual intelligence is determined not by seizures per se but, more importantly, by natural endowment and by the presence or absence of antecedent brain damage. The great majority of epileptic children in the community are mentally as normal as children in general. Thus, of 200 office patients under the age of 15 years given the Stanford-Binet test, the average score was 109. However, social rejection often retards educational progress.

HEREDITY

A desire for progeny is universal and deep-rooted. Parents ask anxiously, "Can our child marry and have children and we grandchildren?" Because answers have been contradictory, we shall present our own data in some detail. These have convinced us that the importance of a transmitted tendency to seizures is no longer in doubt. However, other considerations may neutralize or overbalance this tendency and encourage most epileptics to marry and to rear children.

1. Not epilepsy per se but only a tendency to seizures is transmitted; hence, carriers of the tendency, many times more numerous than those with epilepsy, are genetically much more important.

2. A transmitted predisposition is no more important for epilepsy than for many other diseases, for example, diabetes, hypertension, obesity.

3. Epilepsy is not to be feared as it once was. Successful drug treatment has advanced importantly in recent years and additional gains are

probable. The prevention of brain damage and of acquired epilepsy can be extended.

4. Possession by parents of transmissible mental and physical traits which are desirable may outweigh an undesired tendency to seizures on the part of one parent.

Reassured by these facts, we should vigorously oppose laws which forbid marriage of epileptics. We must, however, search out the facts about heredity uninfluenced by prejudice or emotion.

INCIDENCE OF EPILEPSY AMONG RELATIVES

An excellent monograph about epilepsy has been written by Alström.[1] Alström's Swedish data indicate that heredity is not important in epilepsy. We[2] have studied the family histories of approximately 4,000 epileptic patients. Among the 20,000 near relatives of these patients, the incidence of persons with a history of one or more seizures was 3.2 per cent. Approximately one-half had chronic epilepsy. This 1.6 per cent is an incidence three times greater than the incidence of epilepsy (0.5 per cent) in the population of draft age in the United States. The difference between the findings of Alström and ourselves is explained by the fact that his patients were adults and began to have epilepsy at an older age than ours. Alström publishes the age at onset of his cases for only the small group of fifty-nine with a family history of epilepsy. Epilepsy started in the first decade of life in 22 per cent of his cases and in 47 per cent of our 4,000 cases. Conversely, epilepsy began after the age of 20 in 50 per cent of his cases and in only 24 per cent of ours. Authors are agreed that epilepsy usually begins in childhood; hence, our group should be the more representative.

What is the importance of the age at onset of seizures? Our study demonstrated that the number of epileptic relatives decreased progressively with the increase in age of the patient at the time of his first seizure. Thus, children without antecedent brain damage whose epilepsy began in infancy had nearly five times as many epileptic relatives as those who began to have seizures after the age of 30. If conclusions were drawn from only the latter group, we, like Alström, would discredit the influence of heredity. However, we have also the testimony of twins.

EVIDENCE FROM TWINS

Twins are most important in the study of heredity. We[3] have assembled data on 173 pairs of twins affected with seizures, seventy-seven of these identical and ninety-six fraternal. This supplements a previous report of 122 twins.[2] Among the seventy-seven identical twins, concordance was 70 per cent; among the ninety-six fraternal, it was 12.5 per cent. Among the ninety-eight without evidence of acquired brain damage, concordance was 51 per cent; among the seventy-five with evidence of acquired brain damage, it was 20 per cent. Of the identical twins, fifty-one had no evidence of brain damage that antedated the first seizure, while in twenty-six one of the co-twins had suffered brain damage. Both co-twins were epileptic in 88.2 per cent of the uninjured and in only 34.6 per cent of the injured group. Among all fraternal twins the concordance was 12.5

per cent. This is four times the incidence of epilepsy among siblings of epileptics. Presumably, the unusual hazards of pregnancy and premature birth experienced by twins are responsible.

CONCORDANCE OF SEIZURE TYPES

Personal supervision of all but a few of the twins of this series has permitted extension of the study beyond the simple fact of the presence or absence of a history of seizures. Detailed data appear in a chapter by Lennox and Jolly.[3] Therefore, only a condensed statement will be attempted here.

Twin pairs were divided into two groups. First (Group A) are the identical twins without acquired brain damage prior to the first seizure. Second (Group B) are all other twins. There were 144 pairs with a history of grand mal in one or both. Grand mal occurred in both co-twins in 86 per cent of the twins in Group A and in only 17 per cent of those in Group B. Corresponding concordance for forty-two pairs with petit mal was 83 and 8 per cent, and for the fifty-five with psychomotor seizures, 44 and 14 per cent, respectively. The spread between Groups A and B is greatest for petit mal, the ratio being ten to one in favor of the identical group. Simple petit mal (petite absence) is less likely than other forms of epilepsy to have a neuropathologic background. More detailed study demonstrated that concordance extended even to combinations of seizure forms. Concordance is greater when convulsions are combined with petit mal than when combined with psychomotor seizures. The last named are most likely to be attended by pathologic brain lesions.

CONCORDANCE OF ELECTROENCEPHALOGRAM PATTERNS

The findings with respect to the pattern of electrical discharges support the conception that the electroencephalographic pattern is an hereditary trait[4] and that such discharges when recorded are even more specific and more surely genetic in origin than physical manifestations of epilepsy. Paroxysmal bursts of high-voltage waves, either fast or slow, were seen in the records of 105 twin pairs, thirty belonging to Group A and seventy-five to Group B. Concordance of the type of discharge was 77 per cent in Group A and 4 per cent in Group B, a ratio of 19 to 1. The distinction was most clearly defined for twin pairs with three per second spike-wave discharges. Concordance occurred in fifteen out of sixteen twins of Group A (94 per cent) and in only one out of sixteen in Group B (4 per cent). Slow spike-wave, high voltage slow waves or spike discharges appeared in fourteen twins of Group A. The concordance was 57 per cent. Among the fifty-nine twins of Group B it was 3.4 per cent. Among fifty-two twins whose electroencephalograms were non-specific, being either normal or with only fast or slow background activity, there was an 80 per cent concordance for Group A and 60 per cent for Group B. This minor spread between the two groups points to the relative lack of specificity of minor variations from the normal in electroencephalographic recordings.

Regarding the genetic mechanism involved, data from the fraternal twins point to a simple recessive. Even more convincing is the visual

comparison of the electroencephalograms of identical twins of all seizure types. The transient blackouts of childhood (petite absence) are most clearly genetic in origin. The three males, 3 years of age, without significant family history. Both are subject to frequent febrile convulsions. The discharges were not attended by clinical symptoms.

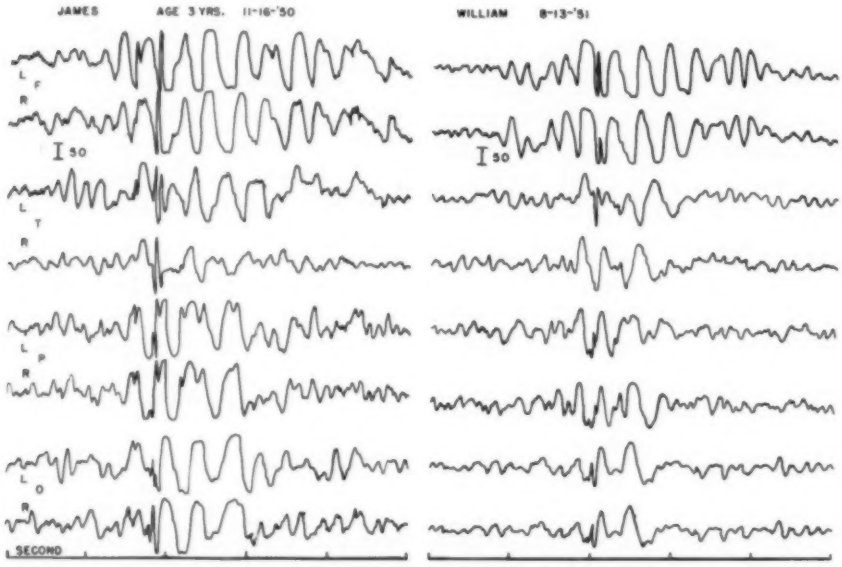

Fig. 5.—The electroencephalograms of twins James and William.

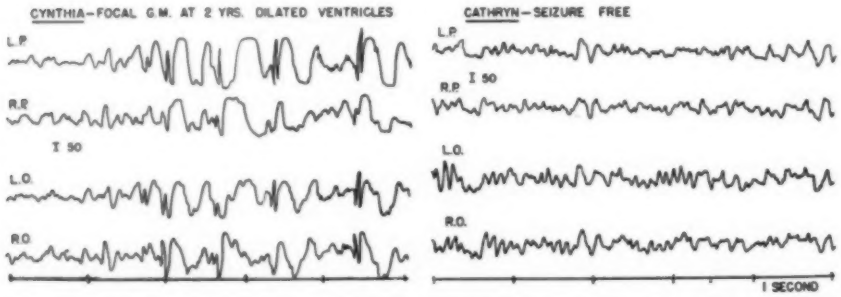

Fig. 6.—The electroencephalograms of Cynthia and Cathryn. (From Lennox and Jolly.[3])

per second spike wave discharges underlie this form of epilepsy. Fig. 5 is a sample of the electroencephalogram of one of the fifteen identical twins with concordance of fast spike-wave formations. The twins are

Among the twenty-four twins in Group B in whom at least one co-twin had a two per second spike-wave discharge in the electroencephalogram, there were four identical twin pairs with a history of brain damage

in only one co-twin. Fig. 6 represents one of these four pairs, twins being 9-year-old girls. Cynthia probably suffered brain injury at birth. She had experienced focal seizures, the pneumoencephalogram disclosed diffuse ventricular dilitation, and her I.Q. was 24 points below her sister's. Her electroencephalogram (left portion) displayed irregularly spaced slow spike-wave formations, whereas the record of the unaffected twin (right portion) was normal.

CONCORDANCE OF INTELLIGENCE

The popular conception that essential (genetic) epilepsy is a brain disorder characterized by mental deterioration is both cruel and unwarranted. Intelligence tests were secured of 130 twin pairs. The results for thirty-six identical twins who had no acquired brain damage are most informative. In these twins, one co-twin sometimes experienced less frequent or less severe seizures than the other. In nine pairs, a co-twin had had either no seizure or only one or two. Yet, the presence of epilepsy or of more severe epilepsy did not lower the average person's I.Q. below the average of the more fortunate co-twin's. However, evidence of an acquired brain damage of the epileptic co-twin was attended by a pronounced lowering of his I.Q.

Either a transmitted constitutional endowment or an acquired brain pathology (or a combination of the two) largely determines the presence and the type of epileptic phenomena, and the person's intellectual performance. Continued studies of patients and their relatives (especially twins) should make these and other matters that concern the epileptic more clear.

CONCLUSION

The interrelationships of emotional and social problems of the child and his relatives call for the best qualities of the pediatrician; versatility, an open mind, persistance in year-after-year follow-up, the quality of hopefulness and courage which is transmitted as by osmosis to the faint-hearted and despondent. The effective doctors will search out the facts about epilepsy and actively combat unfounded fears. Specifically, metabolic (presumably genetic) epilepsy is not related to mental defect. A comprehensive view of the factors of heredity does not preclude marriage and children for most epileptics.

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News and Notes

The following were certified by the **American Board of Pediatrics,** at the examination at Des Moines, Iowa, March 19, 20, and 21, 1954.

Dr. Wallace Roger Anderson, 209 W. Mill St., Austin, Minn.

Dr. Robert Otto Bergan, Duluth Clinic, Duluth, Minn.

Dr. Craig E. Booher, 1810 Wealthy St., S. E., Grand Rapids, Mich.

Dr. Allyn G. Bridge, 301 Kenwood Parkway, Minneapolis 5, Minn.

Dr. Bran Omer Burgert, 915 Medical Arts Bldg., Omaha, Neb.

Dr. John Cadwell Wingfield Campbell, U. S. Naval Hospital, Great Lakes, Ill.

Dr. R. William Carabelle, 2649 Procter St., Port Arthur, Texas.

Dr. Morton R. Crew, 250 N. Water, Decatur, Ill.

Dr. Milton Dodge, 321 Argyle Bldg., Kansas City, Mo.

Dr. Paige B. Follo, 3941 Mosley Dr., Columbus, Ga.

Dr. Stewart L. Griggs, 305 East Walnut St., Green Bay, Wis.

Dr. Aaron Grossman, 1016 Westmoor Rd., Winnetka, Ill.

Dr. John Lemuel Gwinn, 1309 Third Ave., S. W., Rochester, Minn.

Dr. Robert K. Hagan, 10525 S. Talman Ave., Chicago, Ill.

Dr. John W. Harkness, 1411 Wauwatosa Ave., Wauwatosa 13, Wis.

Dr. Joseph Thomas Hart, 1107 S. W. 13th Ave., Portland 5, Ore.

Dr. William Richard Heilig, 1687 Saunders Ave., St. Paul 5, Minn.

Dr. Robert L. Henry, 1701 Pine Valley Rd., Little Rock, Ark.

Dr. James W. Hooker, 602 W. University Ave., Urbana, Ill.

Dr. David Snow Howard, 929 Manor Dr., San Antonio, Texas.

Dr. Rudolph Michael Jarvi, 3051 Congress St., Saginaw, Mich.

Dr. Seymour S. Jurow, Pediatric Clinic, 3345th USAF Hosp., Chanute AFB, Rantoul, Ill.

Dr. Roy C. Knappenberger, 356 N. Parkwood Lane, Wichita, Kan.

Dr. Francis Kodl, 6804 Windsor Ave., Berwyn, Ill.

Dr. William H. Langewiech, 1429 Myott Ave., Rockford, Ill.

Dr. Gilbert Lanoff, 7601 S. Shore Dr., Chicago 49, Ill.

Dr. Charles Austin Leach, 513 S. McKinley Ave., Champaign, Ill.

Dr. Howard E. LeBus, 200 S. Dean St., Gladewater, Texas.

Dr. A. Currie Maimon, 1344 William St., River Forest, Ill.

Dr. Francis Paul Martin, Hq. Med. Det., 1st Cavalry Div., APO 201, c/o PM, San Francisco, Calif.

Dr. William L. Mauran, Jr., 185 Angell St., Providence 6, R. I.

Dr. Jeanne Kehoe, Mercer, 1011 Lake St., Oak Park, Ill.

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Dr. James E. Odell, Dept. of Pediatrics, University Hospitals, Iowa City, Iowa.

Dr. Detlof M. Olson, 953 Medical Arts Bldg., Minneapolis, Minn.

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Dr. Rex Ruppa, 5589 N. Bay Ridge Ave., Milwaukee 11, Wis.

Dr. Robert William Schimmelpfennig, 133 N. Washington St., Marion, Ind.

Dr. George James Schunk, 836 N. W. Sixth, Grants Pass, Ore.

Dr. John Richard Scott, 508 E. 38th St., Indianapolis 5, Ind.

Dr. Alan Cyril Siegel, 545 Lincoln Ave., Winnetka, Ill.

Dr. Rodney M. Smith, Pueblo Clinic, Pueblo, Colo.

Dr. Henry Paul Staub, 3988 Central Ave., N. E., Minneapolis 21, Minn.

Dr. John A. Stedelin, 109½ N. Poplar, Centralia, Ill.
Dr. Jerome Strachman, 4204 N. First St., Cheyenne, Wyo.
Dr. John James Suits, 650 S. Central Ave., Marshfield, Wis.
Dr. David Toll, 3505th USAF Hospital, Greenville AFB, Miss.
Dr. Paul Critchell Tracy, 132 S. Prospect Ave., Park Ridge, Ill.
Dr. Francis Joseph Waickman, 203C Gray Plaza, Apt. 987, Daly-Lewis Acres, Scott AFB, Ill.
Dr. Hobart E. Wallace, 5017th ASU, U. S. Army Hosp., Fort Leonard Wood, Mo.
Dr. Edwin L. Webb, Quarters 605B, Gunter AFB, Montgomery, Ala.

Following is the next oral examination to be held by the Board:

San Francisco, Calif., June 25, 26, and 27, 1954.

Dr. Daniel C. Darrow has accepted appointment to a newly created chair in the Department of Pediatrics at the University of Kansas School of Medicine. He will become Children's Mercy Hospital Professor of Pediatrics on July 1, 1954. Children's Mercy Hospital of Kansas City, Missouri, has been affiliated with the University of Kansas School of Medicine for the purposes of undergraduate and postgraduate education for the past year. Dr. Darrow will have research facilities both at Children's Mercy Hospital and the University of Kansas Medical Center. He will assume his new duties about August 1, after delivering a series of lectures in Paris at the request of the French Government.

The third annual postgraduate conference in pediatrics will be held at **St. Christopher's Hospital for Children,** the Department of Pediatrics of Temple University School of Medicine, from Wednesday, June 9, to Saturday, June 12, inclusive. Information about the course can be obtained by writing directly to Dr. John Bartram, 2600 North Lawrence St., Philadelphia 33, Pennsylvania.

The **National Institute of Mental Health of the Public Health Service** has **Traineeships and Research Fellowships** available in psychology, psychiatry, and allied fields. For example, a graduate of an approved school with a year's clinical internship, who desires to enter the field of child psychiatry, may be awarded a traineeship with a stipend beginning with $2,000 a year and increasing to $3,600 the fourth year. Application must be made through and by the institution where the individual is to take the training, and payments are made through the institution. Full details will be found in a recent bulletin on *Training and Research Opportunities Under the National Mental Health Act,* published by the National Institute of Mental Health, Bethesda 14, Maryland.

The date of the **IV Panamerican Congress of Pediatrics** to be held in São Paulo, Brazil, this summer has been changed from late July to August 1 to 7.

The following communication from the Secretary-General of the **International Paediatric Association** has been received.

1. At the 7th International Congress of Paediatrics in Havana the Executive Board has been newly constituted. According to the "Constitution" three members had to be replaced. Professor F. Gomez and Professor H. F. Helmholz have resigned. They were replaced by Professor Alvaro de Aguiar, M.D., Chief, 5° Distrito de puericultura, Rio de Janeiro, and Dr. E. H. Christopherson, Executive Secretary, American Academy of Pediatrics, Evanston, Illinois. The place of Professor M. S. Maslov, Leningrad, from whom the secretary-general has not heard anything for more than four years, is taken again by Professor A. Wallgren, M.D., Stockholm, until the next international congress.

Copenhagen (Denmark) was selected as the place for the *8th International Congress of Paediatrics.* The president of the congress, Professor P. Plum, M.D., Chief, Paediatric Department, Rigshospitalet, Copenhagen, will be ex officio member of the Executive Board until the termination of the 1956 congress. Professor F. Hurtado automatically resigns after the termination of the 7th International Congress of Paediatrics.

2. The transactions of the 7th International Congress of Paediatrics, Havana, which will comprise three volumes, are being prepared for publication. They will cost about $5.00. As the edition will be limited, all those who are interested in this publication are requested to order it in advance from Professor F. Hurtado, M.D., Hospital Mercedes, Vedado, Havana, Cuba.

Book Reviews

Traité des Cardiopathies Congénitales. E. Donzelot, F. d'Allaines, and associates, Paris, 1954, Masson et Cie, 1106 pages. Price 14,650 fr.

One of the outstanding developments in recent years has been the advances made in the diagnosis and treatment of congenital cardiac disease. In this somewhat monumental volume Professors Donzelot and d'Allaines, physician and surgeon to the Broussais Hospital in Paris, and their associates have brought together not only their own contributions and experience based on over 1,200 cases and 600 operations, but the hundreds of contributions made by workers in many countries. In a first section of 230 pages the authors present a general discussion of such subjects as embryology, etiology, and the various diagnostic procedures as roentgenology, angiocardiography, and physiological methods. In the remaining sections individual conditions are discussed in detail. These are classified into groups as those without a vascular shunt, lesions with an arterial venous shunt, lesions with a venous arterial shunt, and other malformations as anomalies of the coronary arteries. In a final section, tables presenting the frequency, clinical and laboratory diagnostic methods, and prognosis for each condition have been prepared.

While it is impossible to review in detail a volume of this character, a discussion of one chapter will give an idea of the tremendous scope of the text. The 65-page chapter on "Stenoses et Interruptions de l'Aorte" takes up first the history, frequency, embryology, and anatomical-clinical types. It then discusses in some 30 pages the syndrome with collateral circulation and more briefly the syndrome without collateral circulation. The discussion includes numerous drawings and illustrations presenting the roentgenological and angiocardiographic pictures. Finally some 11 pages are given to a discussion of treatment in which the various operations that have been devised to correct the lesion are presented. There is a world-wide bibliography of around 150 references.

The volume will be invaluable to the hundreds of clinics and workers throughout the world who are interested in the subject of congenital cardiac diseases. It is excellently printed in an atlas-sized volume, and has 1,155 illustrations in the form of drawings, photographs, radiograms, electrocardiograms, etc. It represents a tremendous amount of work and knowledge on the part of the authors and their associates.

Medical Progress—1954. Edited by Morris Fishbein, M.D., New York, 1954, The Blakiston Co., Inc., 345 pages. Price $5.00.

A group of nineteen chapters on the progress made in various fields of medicine in 1953 contributed by specialists in the fields of surgery, heart disease, allergy, psychiatry, etc. In a final chapter, Dr. Fishbein summarizes what he considers the most important advances. Among these is Salk's vaccine for polio the value of which has not as yet been tested. In fact, although progress has been made in many fields of medicine, apparently no advances of outstanding importance occurred in 1953.

Congresos de Pediatria de Montevideo, vol. I, Montevideo, 1954, 794 pages.

A volume containing the proceedings of the Pediatric Congress at Montevideo in December, 1951, which also constituted the III Panamerican Congress and the III South American Congress of Pediatrics. In addition to reporting on the membership and those present and the scientific exhibits, some 700 pages of the volume present the papers given at the congress.

Manuel Pratique de Vaccination par le B.C.G. R. Mande, Paris, 1954, Masson et Cie, 200 pages. Price 950 fr.

The text presents in a practical manner the immunological basis of B.C.G. vaccination, the selection of subjects, the differences in techniques that are used, the necessary observation of those vaccinated, etc. In a final chapter the methods and essential rules of procedure are summarized. It is well illustrated with colored plates depicting the reactions to the vaccination.

Editor's Column

THE CHANGING PICTURE OF DISEASE

ONE of the things that makes medicine so interesting to the physician is that it is never static. The important diseases of one era become relatively unimportant in a subsequent era, and new diseases and problems are constantly coming to the fore. There is always something new to investigate and discuss. Nothing illustrates this ever-changing picture better than vital statistics—"the bookkeeping of humanity." It was for this reason that the editor found a recent report issued by the Department of Health of New York City, analyzing the health of New Yorkers in 1953, of considerable interest.

For example, tuberculosis, not so long ago the leading cause of death, has fallen to tenth place as a cause of death. The death rate from all causes has dropped from an average of 18.3 per 1,000 population in the decade 1900-1909, to 10.1 in 1953, although the city has become much more congested and the population doubled. During this time the death rate for infants under one month of age fell from 36.2 to 18.2 per 1,000 births, and the maternal mortality rate from 5.3 to 0.6. The citywide IMR was 24.4 in 1953, with variations in districts from a low of 13 to a high of 40.3.

Some of the figures for the communicable diseases reflect the therapeutic advances of recent years. While 1953 was a low measles year with 3,677 cases without a death, in 1952 there were 34,412 cases without a death. There were 4 deaths from chicken pox in 8,912 cases, and 5 deaths in 2,355 cases of whooping cough. All the pertussis deaths were in infants under one year of age. There were no deaths from diphtheria or scarlet fever. There were only 1,402 cases of scarlet fever in a population of over 8 million people. During the year thirteen outbreaks of communicable diseases in nurseries for newborn infants occurred in thirteen hospitals. Of 321 infants exposed, 97 became ill and 19 died.

The importance of accidents and the need for education in accident prevention is well illustrated by figures in the report. While the total number of deaths in children under 15 for all the communicable diseases was only 159 in 1952, the number of deaths from accidents for children under 15 totaled 296. Of these, 197, or 60 per cent, died as a result of an accident in the home.

Over the years the Health Department of New York City has an outstanding record of progress, service, and accomplishment. Members of its staff, like Dr. Josephine Baker and Dr. William H. Park, have made important contributions to the development of pediatrics in the United States. Beyond question this splendid record of service will continue under the leadership of one of our well-known pediatric colleagues, Dr. Leona Baumgartner, who was appointed Health Commissioner in January.

FAVISM

ALTHOUGH the fava bean is grown quite extensively in a number of parts of this country where there is a large Italian population, favism is an uncommon disease in the United States and not more than a dozen cases have been reported. These have been of a critical type with marked hemoglobinuria, as a rule. Favism, however, exists in moderate and mild forms, and it has been suggested that some of the cases of hemolytic anemias in children of Mediterranean birth or descent diagnosed as some other type of disease may in reality have been cases of favism.[1]

A recent extensive report[2] on favism made to the IV International Mediterranean Congress on Hygiene by Prof. Surinyach of Barcelona, Prof. Marcolongo of Cagliari, and Prof. Alcobe and Dr. Llebaria of Barcelona contains considerable information in regard to the disease and the differences of opinion as to the pathogenesis. Like Cooley's anemia, it is distinctly a Mediterranean disease, and has foci of distribution. Sardinia is the chief center with thousands of cases a year. Other foci are found in Greece, Spain, and probably Italy and Portugal. Sporadic cases are common in these countries and in Turkey and Malta. According to the report, no cases have been reported from Corsica, Egypt, or Syria. The few cases reported in the United States and other countries were in immigrants from the Mediterranean area or their descendants. Thus there is seemingly a constitutional or genetic factor involved in some way.

Many consider the disease to be allergic in character. On the other hand, some question this, and Surinyach points out that the disease is distinctly one of blood destruction without other allergic manifestations, and stresses that other foods will produce what he terms the "alimentary hemolytic syndrome." Marcolongo has found certain toxic substances in the fava bean which act on the red blood cells. Surinyach holds to a dualistic theory as regards the etiology—a direct action of toxic substances in the fava bean on the red blood cells in a susceptible individual.

Clinically we think of favism as an acute condition which may be fatal in children. It follows within a few hours after the ingestion of the bean, particularly the raw bean, with nausea, vomiting, and collapse, and characteristically is associated with hemoglobinuria and jaundice. However, mild ambulatory forms occur, according to Surinyach, with hardly visible hemoglobinuria and jaundice. It is in regard to this last group that confusion may exist in the diagnosis of the cause of anemia in children of Mediterranean descent.

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How MULL-SOY *feeding from birth dispels the shadow of major allergy*

in potentially allergic infants

POTENTIALLY ALLERGIC CHILDREN (offspring or siblings of one or more persons with one or more allergic diseases)	NO. OF CHILDREN	INCIDENCE OF MAJOR ALLERGY TO 6 YEARS
CONTROL GROUP #1* (siblings of experimental group)	65	64.6%
CONTROL GROUP #2* nonrelated; (carefully selected from 4,710 children in 1,215 allergic families for similar parental and sibling allergic backgrounds)	175	52.0%
EXPERIMENTAL GROUP (Cow's milk withheld from birth; 3 breast fed, 5 on meat base formulas, 88 on MULL-SOY; cow's milk introduced later)	96	14.6%

% 10 20 30 40 50 60 70 80 90 100

*Observed for same lengths of time as counterparts in experimental group. Table adapted from: Glaser, J., and Johnstone, D. E.: Prophylaxis of Allergic Disease in the Newborn, J. A. M. A. 153:620, Oct. 17, 1953.

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